

Will the Test Ban Ever Become True ?

THESE are confusing times for those who hope that the partial test-ban treaty will one of these days be extended to cover explosions beneath the ground. In the United States (see page 6) President Nixon seems finally to have agreed to let the underground test in the Aleutians take place. The Joint Committee on Atomic Energy in Washington has also been mulling over the question—the chances are that it will accept the Department of Defense's view that it would be unwise at this stage to extend the partial test-ban. Indeed, the seismologists are understandably divided on the issue—some of those who gave evidence in Washington last week were confident that it would be feasible promptly to extend the test-ban to cover underground tests, but others thought the time had not come. From a strictly technical point of view, this ambivalence is borne out by the 1971 progress report of the Stockholm International Peace Research Institute (SIPRI) on *Seismic Methods for Monitoring Underground Explosions*, Dr David Davies's latest supplement to the first report on seismic detection methods now distributed from Stockholm. The improvements of technique in the past two years have been considerable—new instruments now being laid out should make it possible two years from now to discriminate between explosions and earthquakes by remote methods where the explosions are equivalent to ten kilotons detonated in hard rock. There is even a chance that the limit of discrimination will settle at two kilotons when there is more experience of the advanced instruments.

The Cannikin test in the Aleutians is worrying for several reasons. It will most probably not trigger off an earthquake, and to that extent the Atomic Energy Commission was probably within its rights. The ecological dangers of which people have spoken are themselves ill-defined and improbable, although the way in which the Council on Environmental Quality has declined to comment on the AEC's environmental statement is a slap in the face for those who have been waiting for great things from the council. The real objection to the Cannikin test is political. For one thing, it gives offence to neighbouring countries, Canada and Japan in particular. For another, since it seems to be acknowledged that the test is part of the programme to develop warheads for anti-ballistic missiles, the occasion seems to serve notice that the SALT talks are making less rapid progress than people had been hoping. Dr James Schlesinger, the chairman of the AEC, said last week that he did not expect the tests to affect the talks; most of his listeners will believe that that can be true only if the talks are going badly. It is true, of course, that the Soviet Union has only recently fired an underground explosion in its testing ground at

Novaya Zemlya, so that both partners in the talks seem to be following the same despondent line. Unhappily, even here the facts are not clear. The AEC says that the most recent Russian test was of a weapon with a yield of three megatons or more, but the calibration of the magnitude of the surface waves produced by explosions of different power (reported by Dr P. D. Marshall and his colleagues on page 8) suggests that the Russian explosion most probably had a power less than 1.5 megatons. The amplitude of the surface waves have after all been published. The question in people's minds is bound to be whether the AEC is trying to make five megatons in the Aleutians seem a little more palatable to everybody by exaggerating the size of the explosion.

The difficulty of discriminating between underground tests and earthquakes will, in principle, never be solved. The more sensitive the instruments become, the greater will become the number of tiny earthquakes which they record and the greater will be the possibility that quite small nuclear explosions will go undetected. And it will not be long before instruments are refined to the point at which it will be necessary to distinguish nuclear explosions from other artefacts—ordinary chemical explosions, for example. In other words, there is plainly a limit to the perfectibility of a monitoring system operated by remote control. The practical question is, therefore, to decide at what point in the progressive improvement of seismic detectors it will be best to say that the time has come to settle for a treaty.

What are the risks? The United States Congress and those government departments which fan its suspicions of any agreement that lacks provision for on-site inspection will always of course be able to shelter behind the view that no treaty can bring utter security. Any comprehensive test-ban treaty based on remote control is bound to allow some small explosions to go undetected. The question, from the point of view of the United States, is whether the Russian government has a military need to test weapons with an explosive power of a kiloton or two, whether it would risk the contumely of being discovered by some other method—espionage, perhaps—to have broken a treaty for the sake of such miniscule explosions and whether, in any case, there would be a military advantage in making such tests. After all, the days of the tactical nuclear weapon are over. In short, the point has probably been reached when a slavish insistence on on-site inspection has come to seem an attempt to avoid what could be an exceedingly valuable international agreement. The longer this goes on—and the Soviet government is as much to blame as the American—the more discreditable it will seem.



Alice Economics

Now that Mr Edward Heath has won his majority for the right to spend the coming year battling legislation concerned with the European Communities through the House of Commons, the recriminations are bound to be thrown thick and fast. The oddest so far is from Professor R. S. Scorer, professor of mathematics at Imperial College, London, who was complaining in *The Times* last week that the debate about British entry into the European Communities has ignored "the main issue of our time—how to control the pollution and the population explosion". He went on to say that the chief argument for membership is that it will "make the rich richer", but that "it is very dangerous to commit ourselves further to driving industry forward on those conventional lines which have brought about our predicament. . . . Member countries need to commit themselves as a matter of urgency to stopping the pollution which is rendering every sea around Europe useless in the biological cycle which is necessary for our continued existence. The rosy future in Europe seen by our leading industrialists is short-term only—it is physically impossible for it to endure."

The chief difficulty is, of course, to know whether Professor Scorer wishes to be taken seriously. What he seems to be saying is that even as things are, Europe is heading for a sticky end. If Britain joins the European Communities, as it will (Mr Harold Wilson notwithstanding), then the pace of economic growth will accelerate, the accumulation of pollution will accelerate, and the end will come sooner. This argument is false both in its premises and in its logic. Is it possible that Professor Scorer has been trying to provide the British public, and especially those parts of it which happen to read *The Times*, with a caricature of the arguments now constantly advanced by the environmentalists?

The premises are false in all kinds of amusing ways, but a list of them may help to warn off young people and other innocents. First of all, it is, as Professor Scorer no doubt wished to demonstrate, false to say that economic growth necessarily brings pollution. Indeed, in present circumstances, economic growth is probably a prerequisite for sensible measures for looking after the environment. Is it any accident that the richest nation in the world should now be the one making the most fuss about pollution? Is there anything but economic growth that will allow the people of India to get rid of pollution of the environment by the cholera organism? And if Europe wants to pay more regard to the condition of its environment, will it not be necessary to have at least enough economic growth to pay for all the extra sewage plants and government inspectors that that laudable task will require?

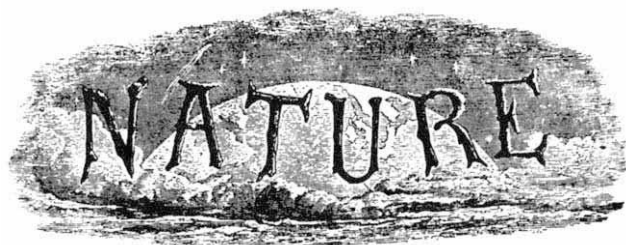
In Professor Scorer's little joke, the second false premise is that pollution is making the European seas "useless in the biological cycle which is necessary for our continued existence". Precisely what form of pollution he has in mind is hard to see. The beaches are more heavily polluted with flecks of oil than they have been for many years: nobody will deny that. But is there any evidence that British waters, say, have been rendered unproductive by pollution? It is true, of course, that herrings are now much harder to come by in the North Sea, but the reason for that is over-fishing. There is a risk that other species

of fish—haddock and cod, for example—will also be damaged in the same way. Salmon are also under pressure because of the new commercial fishery off the coast of Greenland. No doubt there is a great deal to be done to regulate these matters more sensibly, but law and regulations (or the lack of them) seem to be more important causes of potential trouble than pollution.

The belief that a larger European economic unit will "only help to make the rich richer" is of course an ambiguous remark—does Professor Scorer refer to people or to nations? If he has people in mind, there is a wealth of evidence to show that for a single economic unit, economic growth is one of the best ways to a greater measure of equality. If his remark had been intended seriously and had been directed to the gulf between the rich nations and the poor nations, it is hard to see how the emergence of an economically powerful European economic entity would be necessarily a bad thing. But surely what would matter is whether the European Communities would be liberal in their policies on foreign aid.

Professor Scorer's little joke would be harmless enough if it did not use some of the language which is by now widely used by those who seem to think that the world is about to end. That other mathematician, Charles Lutwidge Dodgson, sought to warn his young readers away from ill-defined heresies by means of allegory, but some people think he was too obscure. Professor Scorer's letter to *The Times* may have fallen flat for the same reason, for there will be many who will think he meant it to be taken seriously.

100 Years Ago



From an obituary of Charles Babbage by Professor W. S. Jevons.

Of all Mr. Babbage's detached papers and volumes, it may be asserted that they will be found, when carefully studied, to be models of perfect logical thought and accurate expression. There is, probably, not a sentence ever penned by him in which lurked the least obscurity, confusion, or contradiction of thought. His language was clear, and lucid beyond comparison, and yet it was ever elegant, and rose at times into the most unaffected and true eloquence. We may entertain some fear that the style of scientific writing in the present day is becoming bald, careless, and even defective in philosophic accuracy. If so, the study of Mr. Babbage's writings would be the best antidote.

Let it be granted that in his life there was much to cause disappointment, and that the results of his labours, however great, are below his powers. Can we withhold our tribute of admiration to one who throughout his long life inflexibly devoted his exertions to the most lofty subjects? Some will cultivate science as an amusement, others as a source of pecuniary profit, or the means of gaining popularity. Mr. Babbage was one of those whose genius urged them against everything conducive to their immediate interests. He nobly upheld the character of a discoverer and inventor, despising any less reward than to carry out the highest conception which his mind brought forth.

From Nature, 5, 29, November 9, 1871.

OLD WORLD

EUROPEAN LABORATORY

Italian Threat

THE Italian government has threatened to withdraw from ESRO unless its plans for the future of ESRIN, presented to the ESRO council at its meeting in Paris last week, are accepted. The future of ESRIN has been in the balance since it was announced last July that pure research had no part in the future of ESRO.

The hope that ESRIN can be maintained in its present form comes in a resolution submitted to the ESRO council by the Italian delegation at a meeting held on October 26. The closure of ESRIN would affect the Italians more than any other ESRO member and the threat made by Italy to withdraw from ESRO will possibly change the course of the council's action. The Italian delegation proposed that "... in a spirit of cooperation some of the ESRO buildings should be transferred to Italy and the remaining buildings should house ESRO work devoted to coordination and analysis of data relating to space missions in the scientific and applications field". The threat of withdrawal is made by the delegation when it continues, "It cannot, however, fail to point out that if it were impossible to reach agreement along these lines it would have serious effects on Italian participation in the organization's programmes."

The council has responded to the threat by inviting the Italian delegation to get together with the director general of ESRO, Dr Hocker, in order to set up a working party to investigate the possibility of such an arrangement. The working party is, however, working to a deadline as the proposals made in July are due to be ratified at an ESRO council meeting to be held in late November, and the council has allowed until November 15 for the working party to report on whether the proposed Italian solution is workable.

Scientists at ESRIN are unhappy about the possibility of the laboratory being split as the conditions of employment within ESRO differ considerably from conditions within Italian national laboratories. It remains to be seen that if the Italian solution is the only one put forward whether it will be accepted by the ESRIN scientists.

An assurance was given at the council meeting last week that ESRIN would still be supported by ESRO until the end of 1973. An ESRO spokesman said this week that it was essential for work in progress to be completed and the present budget of \$2 million would be decreased to \$1.5 million in 1972 and \$1 million in 1973. This can be compared with the present ESRO scientific budget of \$27 million.

The staff of ESRIN is naturally embittered at the way the decision was taken to cease supporting the laboratory and this has in no way been helped by the attitude of the ESRO council that has forbidden the ESRIN director and staff members from communicating with the press. That this has irritated Dr N. D'Angelo, the present director, is shown in the following exchange of telegrams between ESRO headquarters at Paris and ESRIN. The following is the text of a message from ESRO in Paris to D'Angelo with a reply sent the following day, October 15.

"In present circumstances the directorate believes that it is preferable not (repeat not) to accord interviews. As you know the situation is still fluid and decisions on ESRIN and other parts of ESRO remain to be taken at the end of November. A full statement will be made at that time and in the meantime director general's policy is not to seek publicity or to reply to provocative articles beyond correcting gross factual errors."

The reply from D'Angelo was: "Ref. your memorandum concerning statements attributed to me. . . . Do not understand how it can be not opportune to correct gross factual errors made in attributing to me some statements which I had not made. Not in real interest of organization, quite apart from fact that my own name has been misused."

There is no doubt that ESRO headquarters in Paris are being unrealistic in hoping that the staff of ESRIN will accept their fate quietly. The scientist will not rest quietly while the door of opportunity is being slammed in his face.

NOBEL PRIZE

Father of Holography

THE 1971 Nobel Prize for physics has been awarded to Professor Dennis Gabor, of Imperial College, London. It comes as something of a surprise that the award is made for Professor Gabor's "invention and development of the holographic method" alone rather than in recognition of his broader contribution to physics. For although Professor Gabor is recognized as the inventor of holography, the technique lay dormant for more than a decade after the invention, first reported in *Nature* (161, 777; 1948). Since then, he has made significant contributions to fields as diverse as electron microscopy and cybernetics.

Born in Budapest in 1900, Gabor studied and worked in Germany until 1933, when he moved to England. The principle of holography which he developed is simple enough—an object is illuminated by a coherent electron or light wave, and the interference pattern resulting from the interaction of the

secondary wave arising from the object with the strong background wave is recorded on a photographic plate. When the plate is illuminated by the strong background wave alone, the information which it contains about the object originally viewed can be extracted to give an image. As is often the case, however, it was a major step to develop practical holography from the first successful laboratory experiments.

Originally, Gabor hoped that holography would offer a new microscopic technique, because micrographs constructed using electron waves but "played back" with an optical synthesizer, should produce an image scaled up in the ratio of light waves to electron waves—some 100,000 times magnification. But this hope was unfulfilled, and the "electron interference microscope" did not then become a practical reality.

The chief difficulty with the Gabor method was the difficulty of separating the information required from a "conjugate wave" which may be regarded as attributable to a fictitious object similar in nature to the true object but occupying a different plane. With the advent of lasers, interest in holography revived because of the availability of coherent sources of optical light. But the technique remained practically unused until E. N. Leith and J. Upatnieks developed an improved wavefront reconstruction technique in the early 1960s. Leith and Upatnieks were also at the forefront of the development of three-dimensional holography.

In spite of practical difficulties, however, the basic principles of Gabor's method remain sound, and in this sense he is truly the father of holography. Indeed, the principle of the electron interference microscope has itself been vindicated. Holographic techniques have now been used by Professor George Stroke and his colleagues to improve the resolution of electron micrographs to 2.5 Å, revealing the internal structure of a virus (*New Scientist*, 51, 671; 1971).

Extract from D. Gabor's original letter describing the technique now known as holography:

"... the arrangement is similar to an electron shadow microscope; but it is used in a range in which the shadow microscope is useless, as it produces images very dissimilar to the original. The object is preferably smaller than the area which is illuminated in the object plane, and it must be mounted on a support which transmits an appreciable part of the primary wave. The photographic record is produced by the interference of the primary wave with the coherent part of the secondary wave emitted by the object. It can be shown that, at least in the outer parts of the diagram, interference maxima will arise very nearly where the phases of the

primary and of the secondary wave have coincided.

"If this photograph is developed by reversal, or printed, the loci of maximum transmission will indicate the regions in which the primary wave had the same phase as the modified wave, and the variations of the transmission in these loci will be approximately proportional to the intensity of the modified wave. Thus, if one illuminates the photographic record with an optical imitation of the electronic wave, only that part of the primary wave will be strongly transmitted which imitates the modified wave both in phases and in amplitudes. It can be shown that the 'masking' of the regions outside the loci of maximum transmission has only a small distorting effect. One must expect that looking through such a properly processed diagram one will see behind it the original object, as if it were in place.

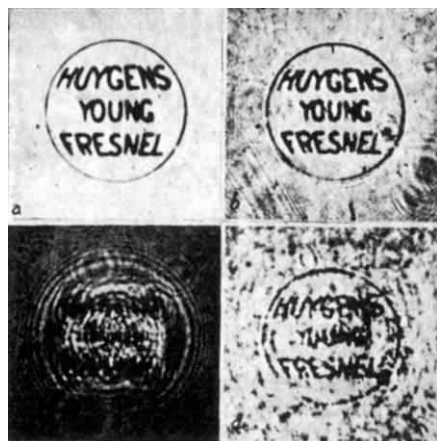


Fig. 2. (a) ORIGINAL MICROGRAPH, 1.4 MM. DIAMETER. (b) MICROGRAPH, DIRECTLY PHOTOGRAPHED THROUGH THE SAME OPTICAL SYSTEM WHICH IS USED FOR THE RECONSTRUCTION (d). AP. 0-04. (c) INTERFERENCE DIAGRAM, OBTAINED BY PROJECTING THE MICROGRAPH ON A PHOTOGRAPHIC PLATE WITH A BEAM DIVERGING FROM A POINT FOCUS. THE LETTERS HAVE BECOME ILLEGIBLE BY DIFFRACTION. (d) RECONSTRUCTION OF THE ORIGINAL BY OPTICAL SYNTHESIS FROM THE DIAGRAM AT THE LEFT. TO BE COMPARED WITH (b). THE LETTERS HAVE AGAIN BECOME LEGIBLE.

"The principle was tested in an optical model, in which the interference diagram was produced by monochromatic light instead of by electrons. The print was replaced in the apparatus, backed by a viewing lens which admitted about $\sin \alpha = 0.04$, and the image formed was observed and ultimately photographed through a microscope. It can be seen in Fig. 2 that the reconstruction, though imperfect, achieves the separation of some letters which could just be separated in direct observation of the object through the same optical system. The resolution is markedly imperfect only in the centre, where the circular frame creates a disturbance. Other imperfections of the reconstruction are chiefly due to defects in the microscope objectives used for the production of the point focus, and for observation.

"It is a striking property of these diagrams that they constitute records of three-dimensional as well as of plane objects."

(From *Nature*, 161, 777; 1948.)

NOBEL PRIZE

Herzberg Honoured

THE 1971 Nobel prize in chemistry has been awarded to Dr Gerhard Herzberg for his work on the electronic structures and geometries of molecules, especially free radicals. Dr Herzberg created the sound basis on which modern molecular spectroscopy is built and it was his own dynamic and enthusiastic approach to the subject which made his laboratory at the National Research Council in Ottawa a mecca for spectroscopists and his books on spectroscopy standard works of reference.

Dr Herzberg was born in Hamburg in 1904 and took a doctorate in physics at the University of Darmstadt in 1928. After two years at the University of Bristol, he returned to Darmstadt where he stayed until 1935. He then spent ten years at the University of Saskatchewan before moving to Yerkes Observatory, Chicago, in 1945. It was there that he applied his spectroscopic expertise to studies of the molecular spectra of planetary atmospheres and, with near infrared absorption techniques, he reproduced many of these spectra in the laboratory using long tubes of gas at high pressures. The period at Yerkes also saw the birth of a fruitful working relationship with Edward Teller which led to the enunciation of the Herzberg-Teller spectroscopic rules.

Although Dr Herzberg is essentially an experimentalist, he has a thorough understanding of the theoretical principles of his work which contributes to the high quality of his three books on molecular spectroscopy. His investigations of the structures of free radicals made extensive use of the technique of flash photolysis and his interest in astrophysics was further stimulated by his study of radicals such as $-\text{CH}$ in the tails of comets.

Dr Herzberg's own achievements are many but his infectious enthusiasm and example must have inspired much more work than he himself has performed.

SPACE

Goodbye to All That

THE successful launch of the technology satellite Prospero on October 28 will in no way affect the decision to abandon Black Arrow announced in July (see *Nature*, 232, 363; 1971). The satellite was launched at 0509 BST from Woomera and went into a near-polar elliptical orbit of 350 by 850 miles. The Black Arrow launcher worked perfectly after the one failure, one success and one partial success that make up its past history, and the experiments on board are all behaving

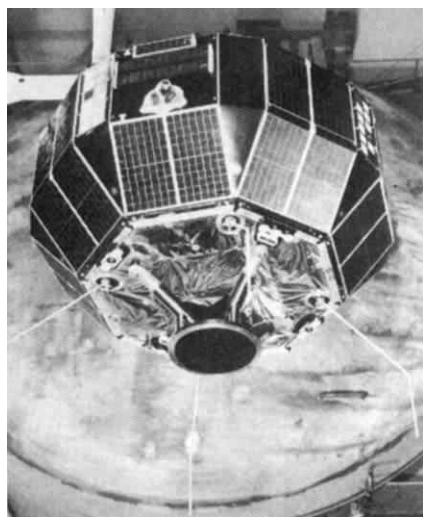
normally. The useful life of the satellite will be between six months and a year, during which equipment for future space vehicles will be tested and a scientific experiment to measure the incidence of micrometeoroids—designed at the University of Birmingham—will be conducted.

Prospero—otherwise known as X3—is the second entirely British satellite to go into orbit, the first being the scientific satellite Ariel 3 in May 1967, but Prospero is the first to go up on a British launcher. The only other satellite at present planned under the national space technology programme is X4 which is due to be launched in 1974 on an American Scout rocket from the United States Western Test Range. Otherwise Britain's national space programme hangs fire until the government's review of it is completed early next year, although the scientific space research programme continues with the launch of UK-4 (Ariel 4), expected at the end of this month.

The decision to abandon Black Arrow was not taken because of the failure of the early launches so much as because the launcher was too small to put more than a low orbiting satellite into space and because of the high cost of the infrequent launches of the rocket. The average cost per launch of Black Arrow has been about £2 million whereas NASA will launch X4 for Britain for £1.25 million. Where the future of Britain's satellite programme may well lie—if it is to have a future—is in the larger geostationary satellites which cannot easily be launched from Woomera but which can be put into space from the USA. Hawker Siddeley, BAC and Marconi are at present studying designs of geostationary technology satellites (GTS).

Meanwhile Britain's active rocket engine industry is confined to supplying Skylark to ESRO and supplying Blue Streak to ELDO on a commercial basis—Britain having effectively withdrawn from ELDO by refusing to support an extension of it in 1968 and limiting commitment to £11 million from January 1, 1969. Further, it is most unlikely that Britain will attempt to develop a new launcher alone but will instead concentrate the limited money available—about £4.6 million a year at present—into British satellites launched from the United States. There is as yet no firm agreement with NASA that American rockets will be available to launch British satellites after X4 but suggestions that such an agreement may not materialize meet with bland assurances that there will be no problem.

Apart from Britain's own satellite work there is the possibility of British involvement in the post-Apollo programme, and both Hawker Siddeley and BAC are studying precisely what con-



Prospero, Britain's first technology satellite, now passing over the whole of the Earth's surface twice every 24 hours.

tribution they could make. Talks between NASA and the European nations, however, have so far produced no firm plans, and British withdrawal from the talks because the areas of co-operation were not sufficiently defined and because of the assumption behind the talks of a link-up between the post-Apollo programme and ELDO's Europa 3, in which Britain has declined to participate, will not have helped speed results.

HISTORY OF SCIENCE

Rutherford Remembered

THE life and work of Ernest Rutherford were recalled last week during the British celebrations to mark the centenary of his birth in New Zealand. A visit to the Cavendish Laboratory and lectures in Cambridge were included in the programme, as well as three lectures at the Royal Society and a Friday Evening Discourse at the Royal Institution that was principally devoted to some of the elegant experiments which Rutherford himself performed.

Sir Mark Oliphant, one of Rutherford's co-workers at the Cavendish Laboratory, spoke at the Royal Society about Ernest Rutherford the man. But before delivering his own address, Sir Mark read some of the notes prepared by Sir James Chadwick who was to have lectured but was prevented from so doing by ill-health. Sir James had been planning to describe his first contacts with Rutherford while attending his undergraduate course on electricity and magnetism at the University of Manchester in 1909. During this time, Sir James recalls that he began "to realize what physics was all about".

Sir Mark Oliphant's own recollections

of Rutherford were of a man who "looked more like a businessman or a Dominion farmer" and who seemed incapable of speaking in anything but loud tones "tinged with an Antipodean flavour". Many of Rutherford's habits were evidently trying for those who worked with him; he apparently possessed no fountain pen and would often perform rapid arithmetical calculations in an illegible fashion or attempt to mark film taken during an experimental run before it was properly fixed or dried. It seems that even Rutherford was criticized in the 1930s by the council of the then Department of Scientific and Industrial Research for not adapting his research to the needs of industry and for producing the wrong type of research worker; the concern about such matters shown by the research councils nowadays is evidently nothing new.

In the afternoon, Sir Harrie Massey sketched the developments during the twentieth century that had been a natural consequence of Rutherford's own work—including the identification of many elementary particles in cosmic radiation and of an even larger number at particle accelerators. Professor N. Feather said of Rutherford, Newton and Faraday that "each was in his own way unique, each in some ways unsurpassed, each a giant in our society's history".

In the best traditions, Dr T. E. Allibone, who also worked under Rutherford at the Cavendish Laboratory, lectured with a liberal sprinkling of experiments based on those performed by Rutherford himself. These included a demonstration of the magnetic deflexion of α -particles, using apparatus that was characteristically Rutherfordian in its compactness. The famous α -particle scattering experiment was shown off to particular advantage with the help of an image-intensifier



Lord Rutherford 1871–1957.

which allowed the scintillations to be displayed on a closed-circuit television screen.

RESEARCH COUNCILS

Riding the Storm

THE Social Science Research Council was particularly concerned with finance during the past year and its plans for increasing support for research and training students received a severe setback when government support for the research councils was cut in the autumn of 1970. Mr Andrew Shonfield, then chairman of the council, says in the annual report that the cuts affected the SSRC more than the other research councils because a greater proportion of the SSRC's money is spent on student support, whereas the other councils could cut long-term projects without affecting postgraduate awards. (*Report of the Social Science Research Council April 1970–March 1971*, HMSO, £1.50.)

The theme of the report is the effect on social science research of the reduced rate of expansion imposed by the government. After the curbs placed on spending in 1970, the council had to restrict the number of studentships awarded in September 1971 to the number allocated a year previously. This reversal of the trend that had seen the number of new studentships increase from 903 in 1968–69 to 1,521 in 1970–71 was implemented by the council in the novel way of requiring third-year research students, who in previous years had their grants renewed automatically if their supervisors' reports were satisfactory, to compete with new research students for the limited number of awards. This approach, predictably, had its opponents in university departments who felt that a person of proven research ability should not have to compete with aspiring research workers, but the council felt that in this way it was being fair to the new graduates and such an approach ensures, of course, that the holders of awards apply themselves during the second year of their research work.

One of the pleasing aspects of the report is that the SSRC has been increasingly absorbed into the scientific community of the other four research councils and the Council for Scientific Policy. The council welcomes the challenge of having to compete with the other research councils for resources and Mr Shonfield looks forward to the day when the SSRC will be an organization that is comparable to the other research councils.

Nearly £2 million was committed by the council during 1970–71 for research in eleven major disciplines. These range from £390,942 allocated to management and industrial relations, to £30,362 allocated to human geography.

NEW WORLD

The Limits of Seismology

by our Washington Correspondent

THE Partial Test Ban Treaty was always supposed to be a temporary expedient—the best that could be achieved at the time. The treaty is now more than eight years old, and attempts to reach agreement on a more comprehensive arrangement have always fallen at the first hurdle—insistence by the US government on on-site inspection and the unwillingness of the Soviet government to consider such a proposal. In the meantime, nuclear weapons testing has continued—the chairman of the Atomic Energy Commission, Dr James R. Schlesinger, was telling the world only last week that President Nixon has now given the green light for the 5 megaton Cannikin test in the next few weeks.

To understand better the basis for the Administration's policies towards a comprehensive test ban, the Joint Committee on Atomic Energy last week held two days of hearings designed to assess the ability of seismologists to recognize signals from underground explosions. Four chief conclusions emerged from the hearings. First, the financial shot in the arm that the Defense Department has given to seismology since the partial test ban has produced some spectacular advances in monitoring techniques, but opinions differ on what can be accomplished. Second, the Administration is not yet prepared to change its views about on-site inspection, and the Joint Committee on Atomic Energy is unlikely to demand such a change of policy. Third, the funding of seismological research by the Defense Department is beginning to peter out. Finally, and perhaps most important, it is becoming increasingly clear that the chief decisions are now political and not technical.

In the past year there have been many claims and counter claims about the ability of seismologists to police a ban on underground testing, and the Defense Department's insistence on on-site inspection has been under increasing fire from some scientists and from the press. Some argue that present techniques and instruments suitably deployed could pick

up all but the smallest explosions (down to one or two kilotons) while others maintain that a determined violator of a comprehensive test ban could use a variety of tricks to hide the seismic signals from even quite large underground explosions.

What is the ability of seismological techniques to discriminate between the signals of small explosions and of earthquakes? Both produce a variety of seismic waves that travel through the Earth and along its surface, but fortunately the signals from the two sources differ in such a way that it is usually possible to tell them apart. The most promising technique so far seems to be to measure the proportion of energy generated in the form of short period body waves (m_b) and long period surface waves (M_s). In general, earthquakes are more efficient generators of surface waves than are explosions.

There is a limit to which any technique is capable of picking up signals from either earthquakes or explosions, and that is regulated by the ever present background "noise"—signals from a variety of sources such as ground slippage, wind or traffic near the seismometers. This noise produces a constant interference signal which effectively masks the seismic traces from explosions or earthquakes equivalent to about one-half kiloton set off in hard rock. This has two important consequences—any test ban treaty would have to be undertaken with the knowledge that a violator could explode a very small weapon without fear of detection and that he may also be able to mask the seismic effects of larger devices so that they too would be lost in the background noise.

Another consequence of this theoretical detection threshold is that the body waves from a small underground explosion might be picked up by seismometers while the surface waves would be lost in the noise. In other words, a positive identification of an explosion as opposed to an earthquake may have to rely on the fact that surface wave signals are not detected. Asked last week whether he thought such a no-detection

criterion to be a reliable basis for a comprehensive test ban, Dr Stephen J. Lukasik, director of the Defense Department's Advanced Research Projects Agency (ARPA), which has been responsible for the seismic detection programme, said that he believes not. The Defense Department's line therefore seems to be that positive identification of an explosion should rely on traces of both the body and surface waves—a criterion that raises the identification threshold considerably, and inhibits the likelihood of negotiating a treaty.

That apart, just how capable are present techniques of detecting explosions? That, at least, was what the Joint Committee on Atomic Energy was concerned to find out. Lukasik did not commit himself to any figure for the capability of the present system, but said "we understand how to identify explosions down to m_b 4.5" (equivalent to about five kilotons fired in solid rock) and that "in principle, seismic discrimination around m_b 4.0 appears feasible". This would take the level of explosion that could be detected by improving the seismic arrays down to about one or two kilotons in solid rock. But Dr Lukasik was quick to point out that not all the theoretical problems are yet solved. Explosions at that level would also be detected by the absence of visible surface waves. Dr Eugene Herrin later told the committee that we cannot at present "design an optimum seismic network nor can we reliably estimate the unilateral identification capability of a given network for events of magnitude less than about 4.75".

On the other hand, some seismologists argued at the hearings that a seismic array system can now be designed to monitor explosions down to one or two kilotons, and that such an array would be an adequate basis for policing a treaty banning underground testing. This argument has, in fact, caused considerable embarrassment to the Defense Department since it has been well aired in the press, and it has been billed as the conclusion of a meeting sponsored last year by ARPA. Moreover, in July

this year, the Canadian delegation to the Committee on Disarmament seemed to be saying much the same thing.

One particular point that worries the Joint Committee on Atomic Energy is the extent to which a signatory of a comprehensive treaty could cheat with impunity. Witnesses last week faced a number of questions designed to ascertain the level to which this could be done. The committee was told that there are four potential methods by which a violator could hide signals from relatively large explosions in the background seismic noise. The signals could be damped by firing explosives in alluvium instead of solid rock or, by firing a device in a large cavity (uncoupling), it may be possible to fire off several devices in succession and so generate waves that look like an earthquake, or alternatively, a large device could be set off in the wake of an earthquake, and the seismic waves would be hidden.

Of these methods, only firing in alluvium has been extensively tested, and it is generally agreed that a 15 kiloton shot in alluvium would give about the same seismic signals as a one or two kiloton shot in hard rock. Uncoupling has only been tested once with a 0.3 kiloton explosion, but in theory it may be possible to hide an explosion of up to 100 kilotons by this method. Ripple firing has never been tested, and there are considerable doubts about its potential. Finally, hiding in an earthquake would not be a very practical alternative since it would entail sitting around with a device waiting to be set off until a suitable earthquake comes along.

Perhaps the most important unanswered question that came up in the hearings last week, and one which was not well dealt with, was what happens now with the ARPA seismic detection programme? Started in 1959, Project VELA, as it is known, has been responsible for the infusion of some \$160 million into seismology.

There are essentially three options now open—to do nothing further on seismic detection and identification, but to concentrate on analysing the data from the three large arrays recently deployed in the United States and Norway (the LASA short period array in Montana, the ARPA long period array in Alaska and the NORSAR short period array in Norway), to upgrade the present system, or to push ahead with deployment of a full-scale monitoring system. Which option the government will take is now a political rather than a technical decision.

All three alternatives were mapped out by witnesses last week. A surveillance system based on the present reporting network would consist of selected stations of the Worldwide

Standard Seismograph Network together with the three large ARPA arrays. At a very small cost, this system could be upgraded by the inclusion of five British array stations in Australia, Canada, Scotland, India and Brazil.

The most grandiose proposal was put to the committee by Dr James Brune, professor of geophysics at the University of California, San Diego. Brune's proposal, which apart from increasing the potential to detect small yield explosions would be a bonanza for geophysics, was endorsed by a list of names that looks like a *Who's Who* of geophysics. The proposal, which could be implemented in two stages costing \$27.5 million and \$106 million respectively, consists of large and medium aperture arrays in Europe and Asia, long and short period seismographic stations in Europe and North America, ocean bottom seismographs, and upgraded Worldwide Standard Seismograph Network stations. Such a system, Brune claims, would be able to detect and identify explosions equivalent to 2 kilotons in hard rock, without a serious false alarm problem from small earthquakes being misidentified as explosions. To judge by the questions from the

members of the committee, it seems that they have no intention of rushing to buy the proposal.

Whatever array systems are deployed, the possibility of a violation of a comprehensive test ban treaty being undetected can never be reduced to zero. That is the chief reason why the US government has always insisted on the necessity for on-site inspection, and that is one reason why the Joint Committee on Atomic Energy has tackled a difficult problem. Some witnesses suggested last week, however, that on-site inspection may be a red herring, for not only would very small explosions go completely undetected, thereby providing no grounds for inspection in any case, but, as Lukasik himself admitted, on-site inspection would not necessarily provide evidence of a test.

The decision is now clearly a political one, and it must rely in part on the strategic advantage likely to accrue from testing the very low yield weapons that would not be picked up by seismographs. In his opening remarks last week, Melvin Price, the committee chairman, said that such issues may be explored in later hearings. It now seems that such hearings are vital.

NAS

Thorns in the Academy's Flesh

by our Washington Correspondent

RICHARD C. LEWONTIN, who resigned from the National Academy of Sciences in April in protest against the academy's acceptance of work on projects classified as secret, has been given a full year in which to change his mind. At a business meeting last week, attended by between 70 and 80 of the academy's 900 members, it was decided to postpone action on Lewontin's resignation until the annual meeting next spring. Technically, therefore, Lewontin remains a member of the academy—a situation which he described in his letter of resignation as repugnant.

Why has the academy not decided to let him leave without demur? The chief reason for postponing action on his resignation last week was that the academy has in the past few months moved some way towards meeting the objections raised in Lewontin's letter of resignation. Essentially, Lewontin was concerned that members of the academy are ultimately responsible for all work carried out in the academy's name, and that the acceptance of classified work therefore puts the members in the position of being responsible for reports that they are prevented even from seeing. A provision adopted at the August council meeting now requires

that all academy reports should include a statement to the effect that only the members of the committee producing the report are responsible for its contents.

The academy has decided to see whether such a provision is a sufficient concession to enable Lewontin to remain a member. Lewontin's stand on classified research was endorsed by a few younger members of the academy, three of whom—Thomas Eisner and Bruce Wallace of Cornell University and Robert MacArthur of Princeton—said they would resign if the issues raised by Lewontin were not soon resolved. Asked last week whether the academy's concessions were enough, Eisner said that he at least would probably be satisfied, but added that he did not know the full terms of the provision.

Lewontin has also been critical of the academy's machinery for electing its officers, and this too has been liberalized, but according to Allen V. Astin, the academy's internal secretary, not simply in response to Lewontin's attacks. The chief change agreed at the meeting last week was that officers will in future be elected by a ballot among all members, not just those present at the annual meetings. It is also agreed that nominations can come from the floor of the

annual meeting. In the past, a special nominating committee, appointed by the president with the advice of the council, has produced a slate of nominations that were then voted on by the members present at the annual meeting. (On at least one occasion in the past, however, the election of Dr Detler W. Brook as president in 1950, an unofficial nomination from the floor has carried the day.) In future, the nominations committee's list of candidates can be augmented by suggestions from the floor that are backed by at least seven members.

Another issue raised at the meeting last week has now become a regular

feature of academy meetings. The membership voted down without debate a motion by William Shockley asking that the academy should arrange for a review of the facts relating to the genetic basis of intelligence. Shockley, who won the Nobel Prize for his work on transistors, has consistently tried to steer the academy into seeming to support his belief that blacks are genetically less intelligent than whites. He first tried to get the academy to sponsor a study of the genetic basis of intelligence as long ago as 1966, and in spite of being repeatedly snubbed by votes in the academy's meetings, he has been consistent in his efforts.

Shockley said last week that he introduced the motion at the spring business meeting because he believed that a report conducted by a special NAS committee under the chairmanship of Kingsley Davis had produced weak conclusions. He believes that the time is now ripe for the academy to produce a much more positive report, and presented evidence to the spring meeting to support his belief. His motion was, however, tabled because the paper containing his supporting evidence was presented two days after his motion, and members felt that they should hear his evidence first. Shockley will no doubt be at it again in April.

Surface Waves from Underground Explosions

SEVERAL authors^{1,2} have published data on the surface wave magnitude (M_s) and yield (Y) for underground explosions at test sites in North America. Fig. 1 shows the dependence of M_s on yield for all test sites for which we could obtain explosion yield data. The details of the explosions are given in Table 1. From Fig. 1 it is clear that for explosions in consolidated rock (tuff, salt, granite, andesite and sandstone) all the observations lie close to the line

$$M_s = \log Y + 2.0$$

for yields from 4 kton to 1,300 kton. Only for Discus Thrower and Duryea does the observed value of M_s deviate by more than 0.3 magnitude units from this line, so only for these explosions would the yield estimated from M_s differ by more than a factor of 2 from the published yield. For explosions in unconsolidated rock (alluvium) the curve of M_s against yield seems to be more like

$$M_s = \log Y + 1.0$$

at least for yields less than 100 kton, but more data are required to define this curve. The M_s values plotted in Fig. 1 are means of individual station determinations of M_s , each of which is corrected for deviations of the source to receiver path from an average path. After correction, the standard deviation (SD) of an observation for a given explosion is usually 0.25 magnitude units and the SD on the mean value of M_s is about 0.1. Corrections are applied for the effect of the path on the propagation of surface waves of different periods. Over short paths in North America, for example, the large amplitude pulse-like arrival observed on wide-band long-period instruments is made up of period components close to a minimum value in the group velocity curve. This apparent large amplitude is due to the path and not to the source; the path effect can be estimated as a function of frequency and a correction determined (P. D. M. and P. Basham, to be published). It should be pointed out that path corrections are significant only for short transmission paths over which there is little dispersion. If these transmission path

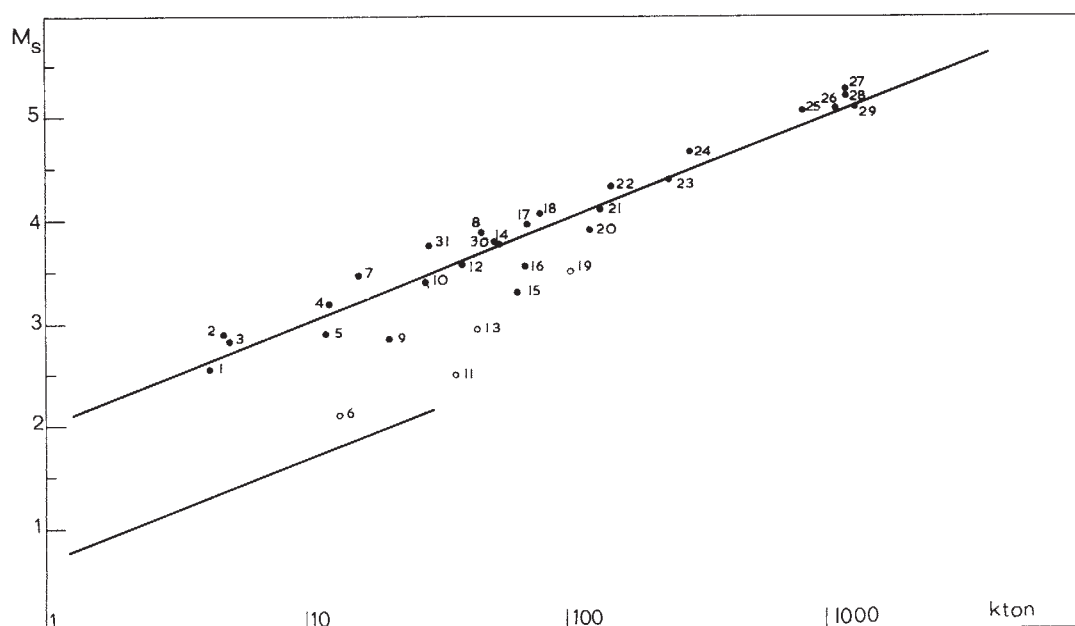


Fig. 1 Surface wave magnitude (M_s) against yield (kton) for explosions in various parts of the world.

Table 1 Details of Some Underground Explosions

Event No.	Date	Name	Region	Medium	Yield (kton)
1	April 14, 1965	Palanquin	Nevada	Rhyolite	4.3 *
2	February 15, 1962	Hardhat	Nevada	Granite	4.8 *
3	October 22, 1964	Salmon	Mississippi	Salt	5.3 *
4	October 26, 1963	Shoal	Nevada	Granite	12.2 *
5	November 5, 1964	Handcar	Nevada	Dolomite	12 *
6	December 3, 1961	Fisher	Nevada	Alluvium	13.5 *
7	February 24, 1966	Rex	Nevada	Tuff	16 *
8	September 30, 1966	Bukhara I	Bukhara	Clay	30¶
9	May 27, 1966	Discus Thrower	Nevada	Tuff	21 *
10	December 10, 1967	Gasbuggy	New Mexico	Shale	29 *
11	October 9, 1964	Par	Nevada	Alluvium	38 *
12	September 10, 1969	Rulison	Colorado	Shale	40 *
13	June 27, 1962	Haymaker	Nevada	Alluvium	45.5 *
14	June 2, 1966	Piledriver	Nevada	Granite	56 *
15	April 14, 1966	Duryea	Nevada	Rhyolite	65 *
16	May 6, 1966	Chartreuse	Nevada	Rhyolite	70 *
17	May 26, 1967	Knicker Bocker	Nevada	Tuff	71 *
18	October 29, 1965	Longshot	Aleutians	Andesite	85 *
19	July 6, 1962	Sedan	Nevada	Alluvium	100 †
20	January 15, 1965	Kazakh	Kazakh	Sandstone	125 ‡
21	February 27, 1965	Saphir	Algeria	Granite	135 §
22	May 23, 1967	Scotch	Nevada	Tuff	150 *
23	September 13, 1963	Bilby	Nevada	Tuff	250 *
24	June 30, 1966	Half Beak	Nevada	Rhyolite	300 *
25	December 20, 1966	Greeley	Nevada	Tuff	825 *
26	December 19, 1968	Benham	Nevada	Tuff	1,100 *
27	April 26, 1968	Box Car	Nevada	Tuff/Rhyolite	1,200 *
28	October 2, 1969	Milrow	Aleutians	Lava	1,200 ¶
29	March 26, 1970	Handley	Nevada	Mesa	1,200 ¶
30	May 1, 1962	Beryl	Algeria	Granite	52 **
31	May 21, 1968	Bukhara II	Bukhara	Salt	47 ¶

* Ref. 10; † *Vela "Uniform" Information Digest*, 2, No. 11; ‡ inferred from *New Scientist*, May 19, 437 (1966) and ref. 13; § ref. 9; ¶ press reports; ¶ inferred from press reports and ref. 11; ** ref. 12.

corrections are not applied, the data do not display a consistent relationship between M_s and yield when data from different test sites are combined.

Theoretical curves of M_s against yield computed using the theory described by Hudson^{3,4} and using the explosion source functions of Haskell⁵ are also shown in Fig. 1. These theoretical computations have also been corrected to an average crust. For consolidated rocks, the fit of the computed curve with the observations is very good; for unconsolidated rocks the predicted value of M_s for a given yield seems to be rather low. (Theoretical predictions were only made up to 30 kton in unconsolidated rocks because this is approximately the maximum yield for containment in a surface layer of alluvium 0.5 km thick—the depth of the alluvium layer in the crustal model of the Nevada Test Site⁶.)

From the data presented in Fig. 1 we conclude that, provided one assumes that explosions at any location have been fired in consolidated rock, yields can usually be estimated to within a factor of two. This is a great improvement on routine calculations using body wave magnitude. For example, the body wave magnitudes (m_b) of the MEDEO explosions (1.6 kton and 3.7 kton chemical explosions) were 5.0 and 5.2 respectively at Eskdalemuir (EKA)⁷ whereas the value of m_b for the 40 kton Rulison explosion in Colorado was found to be 4.7 at EKA⁸. Fig. 1 also shows that the use of the $m_b:M_s$ criterion⁹ to identify explosions at the teleseismic detection limit of $M_s \sim 2.5$ implies yields of about 40 kton in dry alluvium and 3 kton in consolidated rock. Long period arrays on low noise sites are required to record such low

magnitudes at distances greater than 15 degrees from the firing site.

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NEWS AND VIEWS

Unravelling the Chromosome

JUST as the structure of DNA was the basic problem which had to be solved before molecular biology could become a meaningful discipline, so the structure of the eukaryotic chromosome is the vital issue which must be resolved before research today in cell biology can produce a coherent set of concepts instead of a mass of unrelated data. In his article on page 25 of this issue of *Nature*, Dr Francis Crick sets out his ideas on how DNA may be arranged in the chromosomes of higher organisms and what implications his model has for the control of the expression of eukaryotic genes.

The nub of his proposal is that the sites in eukaryotic DNA which are recognized by regulator molecules are not double stranded but comprise single stranded regions of unwound DNA. The nature of the regulator molecules which must interact with the control elements of DNA is unknown. But if they are RNAs, it makes obvious sense for the recognition sites to be single stranded regions of DNA with which complementary base pairing can take place. Because the active sites of proteins tend to be cavities within the molecules rather than protuberances out of them, it would also be easier for a protein regulator to recognize specific sequences of single stranded nucleic acids; the distinguishing groups on the base pairs of duplex DNA are located within grooves but are more readily accessible when the strands are unwound. (In bacteria, of course, proteins seem to manage to recognize specific sequences of duplex DNA.)

One of the most awkward facts to account for when analysing the heredity of higher organisms is their great excess of DNA; the amount varies with the species, of course, but there always seems to be far more DNA in the genetic material of eukaryotes than can be accounted for by adding up the number of genes needed to code for proteins. Dr Crick takes the line that the function of most of the DNA is to regulate the activity of the rest; compact "globular" DNA, which includes the unwound sequences, forms by far the greater fraction of chromosomal DNA—it is the more extended but much smaller fraction of "fibrous" DNA, taking up the conventional duplex structure, which codes for proteins.

What is the relationship of the control elements to the coding fractions? No matter what is the precise packing of DNA within the chromosome, it seems likely that it is one long molecule, running continuously from one terminus to the other. Sequences of control DNA will alternate with sequences of coding DNA. The manifestation of this model, Dr Crick proposes, is seen in the salivary glands of Diptera, which contain polytene chromosomes (made by a many-fold replication of the normal chromosome); under the microscope, large bands containing most of the DNA (the putative control elements) alternate with the much smaller interbands (the coding regions).

Why should so many regulators be needed to control the much smaller number of coding genes? There is no clear answer to be found for this question at present, but Dr Crick points out that the structures needed to maintain

unpaired DNA cannot be constructed on too mean a basis. Another reason may be that a very precise quantitative control is required; it is unlikely to be sufficient just to switch genes on or off. Whenever a gene is to be expressed in some particular type of cell, therefore, its protein product may be synthesized to different extents. One control element might be needed for each type of cell in which the gene is to function.

To unwind DNA, of course, needs energy. Dr Crick points out that when large numbers of different control sequences need to be recognized it may nevertheless work out best to unwind the double helix before recognition. What unwinds the DNA? Dr Crick proposes that chromosomal proteins will achieve this and names the histones as his most likely candidates for the job. Unwinding might result from the formation of some complex structure in three dimensions, or instead it might perhaps be assisted by specific "unwindase" protein(s). The bacteriophage T4, of course, specifies as the product of its gene 32 a protein which seems to have the function of unwinding DNA for replication and recombination. Similar proteins probably assist meiosis in higher organisms; whether they are also present in somatic cells is an open question.

How do the regulator elements function? Dr Crick's model is compatible with either positive or negative control or both—RNA polymerases might recognize promoter-like sites or repressor molecules might recognize operator-like sites. What is the structure of the globular regions? Only some of their DNA will be unpaired; the conventional duplex segments could have a topological role or might perhaps be concerned with producing the regulator molecules themselves. Dr Crick does not say whether only the fibrous regions can be transcribed to RNA; the proportion of globular DNA is so great that it would be surprising if its only function were passively to be recognized. What are the proportions of regulator sites which comprise recognition elements and sites which code for regulator molecules is another unanswered question.

Dr Crick's article provides a chromosome structure to go with control models which suppose that each coding gene is accompanied by a long sequence of DNA concerned with regulating its functions; the best known model of this sort is, of course, that of Britten and Davidson. It will obviously be difficult to gather evidence either to support or to refute Dr Crick's model, but his prediction that globular regions contain single stranded DNA provides the most obvious handle with which to tackle the problem. And if chromosomes do prove to contain extensive amounts of single stranded DNA, models for the coiling of the nucleoprotein particle may need to be rethought.

As Dr Crick himself says, this model raises as many questions as it answers. It will nevertheless serve a valuable purpose if it focuses attention of cell biologists on the critical questions which need to be answered. Unhappily, it is not obvious how this will be done.

Water on the Moon and the Apollo Programme

SPACE enthusiasts must be regretting that the report of what may be molecules of water emanating from the surface of the Moon did not come sooner. It is much too late to save the two Apollo flights that were cut from the programme last year amid uproar from lunar scientists. And it is now unlikely that the second of the last two Apollo flights, Apollo 17, will also be docked from the programme, contrary to what the pessimists were saying a year ago. But the hypothetical water has surfaced just in time to participate in the debate on the need or otherwise to continue the exploration of the Moon after Apollo 17.

In these circumstances the announcement by Dr John Freeman of Rice University, Houston, was bound to be cheering news for the space zealots. To them, the approximately two pints of water which are estimated to have been responsible for the observations imply that the Moon may contain some of the basic raw materials that would have to be ferried there if a scientific colony is to be established. It remains to be seen, however, whether Dr Freeman and his colleagues are raising false hopes. The cloud of gas identified as containing water molecules was recognized in data obtained on March 7 by the suprathermal ion detectors left at the sites of the Apollo 12 and 14 landings. The cloud seems to have been triggered by a series of seismic events. But Dr Freeman is reported to have said that although water vapour is the most probable explanation of the readings, any of several less surprising gases such as ammonia, neon or other rare gases could also have been responsible.

On this basis it would be a mistake if the possibility of large amounts of water trapped beneath the lunar surface were to colour the exploration of the Moon in the same way as the possibility of living material on Mars has been a chief consideration in the design of planetary probes. For the present, the outcome of Freeman's announcement will be to focus attention on equipment to be carried on the Apollo 17 flight to examine the

electrical properties of the surface layers of the Moon, which could conceivably reveal the layer of subsurface ice or water.

In the long term, however, it would also be risking disappointment to use the hypothetical water as an apologia for the continuation of lunar exploration after Apollo 17. While officials of NASA have been stumping the country for the support which they hope will prevent the shuttle programme from suffering the same fate that befell the supersonic transport, many scientists, inspired by the outcome of the Apollo programme, have been living in the hope of funds for a modest continuation of manned lunar exploration when the Skylab experiment is over in 1973. Even without the equivocal evidence for lunar water there should be no shortage of justifications for, say, the launch of a manned and heavily instrumented Apollo spacecraft into a polar orbit around the Moon.

The view that space research after

1973 should continue to concentrate on the Moon will not go unchallenged. Many people would rather first of all ensure that there is enough money in the scientific budget of NASA to follow up the amazing series of discoveries by the X-ray astronomy satellite. This is why the Space Board of the NAS has given priority to the automatic observatory carrying X-ray and γ -ray equipment and scheduled for launch in 1975, rather than to the Grand Tour probes to the outer planets. Indeed, there are signs that NASA has come to terms with the doubts that have been expressed about the Grand Tour, which also include the difficulty of constructing planetary probes that will have to be an order of magnitude more reliable than the present Mariner series. Studies are under way to see what could be salvaged from the Grand Tour project—once considered essential for NASA's well being in the late nineteen-seventies—if it has to be cancelled.

DNA REPLICATION

Restarting Replication of the Bacterial Chromosome

from our Cell Biology Correspondent

WHEN an episome such as the sex factor F, or a lysogenic bacteriophage, becomes integrated into a bacterial chromosome it is replicated passively along with the rest of the bacterial genome of which it is now part even though F factors and the genomes of lysogenic phages carry genetic determinants capable of controlling and initiating their own independent replication. Apparently these genes which function when the F factors or phages exist in an autonomous state become subordinated to their counterparts in the bacterial chromosome upon integration. But what happens when the phage or episome is integrated into the chromosome of a temperature sensitive mutant bacterium which is unable to initiate the replication of its genome at some nonpermissive temperature? Can the replication machinery of the episome or prophage as it were take over and initiate the replication of the entire bacterial chromosome? The answer to this intriguing question, no doubt much

to the gratification of Jacob, Brenner and Cuzin, the postulators of the replicon theory, is that it can.

Earlier this year, Nishimura, Caro and Berg (*J. Mol. Biol.*, **55**, 441; 1971) reported that when an F factor integrates into the chromosome of CRT46 cells—a mutant strain of *Escherichia coli* which is unable to initiate the replication of its DNA at 42° C—the bacteria become Hfr and can replicate their DNA at this temperature. This "integrative suppression" by F factor of the temperature sensitive lesion in CRT46 cells indicates that the entire bacterial chromosome has in effect become part of the F factor replicon.

Now in the latest issue of the *Proceedings of the US National Academy of Sciences* (**68**, 2407; 1971), Lindahl, Hirota and Jacob report that the replication of the *E. coli* chromosome can come under the control of prophage P2 genomes. The Paris group, having found that P2 replicates in CRT46 cells

at 42° C, and therefore has its own genetic machinery for initiating DNA replication, set about isolating mutants of this phage which by lysogenizing CRT46 cells can cause the cells to replicate at 42° C. Exploiting a strain of P2 known as P2tsD₄₆, which specifies a temperature sensitive repressor and cannot complete its replication at 42° C because of a block in the maturation of phage tails, they obtained lysogens of CRT46 and selected for cells which would grow at 42° C. A few of the cells which survived this selection were found to liberate phage particles one strain of which was studied further.

This phage which suppresses the T46 mutation when it lysogenizes carries a third mutation, *sig*₅, which by three factor crosses has been mapped on the phage P2 genetic map and has been shown to be an insertion. This phage integrates at several sites in the *E. coli* chromosome and when it is at least one of these sites the T46 mutation is suppressed. Furthermore, in a series of elegant crosses Lindahl *et al.* have established that a protein specified by the gene *A* of P2 is required to suppress the T46 mutation and allow the cells to replicate their DNA at the nonpermissive temperature, 42° C. This *A* protein is probably essential for the initiation of DNA replication and biochemists eager to come to grips with this process would dearly like to get their hands on it. But it has one tantalizing property; it is a *cis* acting protein and probably cannot be investigated by any sort of complementation analysis because it only acts on the genome which specified it. The biochemistry of DNA replication retains its secrets.

MEMBRANES

CMF Controls Mg Flux

from our Membrane Correspondent

WHEN cytoplasmic macromolecular fraction (CMF) was first described by Loh *et al.* (*Biochemistry*, 7, 726; 1968), it did not seem to be of more than passing interest, because it was only reported as affecting the oxygen consumption of dinitrophenol (DNP)-inhibited mitochondria. Later it transpired (Kun *et al.*, *ibid.*, 8, 4443; 1969) that CMF also prevented the loss of magnesium ions from DNP-inhibited mitochondria. Binet, Gros and Volfin (*FEBS Lett.*, 17, 193; 1971) and Binet and Volfin (*ibid.*, 197) now report significant progress towards the determination of the structure of CMF and ascribe to it a more universal role in membrane function.

CMF (now called cytoplasmic metabolic factor) in common with many substances of profound biological activity is present in tissues at very low concentrations. From 5 kg of porcine liver, Binet *et al.* eventually obtained 1.5 mg

of CMF, but it was not possible to assay its purity because they were unable to get it to migrate in the thin-layer chromatography systems used. Their analytical results suggest that CMF is a water soluble, acidic cyclic peptide of twenty amino-acid residues, sixteen of them different. The water solubility and amino-acid composition indicate that there is little similarity between CMF and cyclic peptides such as gramicidin-S or alamethicin which can act as ionophores (that is, promote the transport of ions) in membranes. Indeed, the chief effect of CMF is to inhibit the movement of magnesium ions across membranes. Apart from confirming that CMF prevented the leakage of magnesium ions from mitochondria, Binet and Volfin also found that CMF

prevented the light-induced ejection of magnesium ions from chloroplasts and inhibited the lethal ejection of magnesium ions from *Escherichia coli* which had been treated with the drug 'Levallophan'. They also found that CMF promotes the uptake of calcium ions by sarcomeres but unfortunately do not report whether CMF affects the transport of ions other than magnesium or calcium.

Thus the role of CMF is apparently to control magnesium and calcium fluxes across biological membranes. How it achieves this at the molecular level is at present unclear and is likely to remain so until more is known about ion transport mechanisms in membranes. CMF may prove, however, to be a useful tool in elucidating these mechanisms.

Magnetic Variations in Columnar Basalts

COLUMNAR basalts have seldom, if ever, been used for palaeomagnetic purposes, partly for the obvious reason that they occur only infrequently but partly because their peculiar structure induces the suspicion that directions of magnetization may be dependent on factors other than ancient field directions. This suspicion was largely confirmed by Symons (*Geophys. J.*, 12, 473; 1967) from a very thorough study of a single column from the Giant's Causeway, Northern Ireland, which showed that not only palaeomagnetic properties but also inherent magnetic properties vary greatly throughout a column.

It seemed to Symons that the varying magnetic properties (natural remanence, Curie point, coercive force, bulk susceptibility, saturation magnetization and others) are essentially those which depend on the compositions of the titanomagnetites present and that such compositional variations as there are arise from differences in oxygen rather than from titanium content. And because such magnetic and compositional variations are likely to be the result of the unusual method of formation of columnar basalts, study of these variations could help to solve the vexed question of just what this method is.

Similar conclusions have now been reached by Radhakrishnamurty *et al.*, who in next Monday's *Nature Physical Science* report a study of some of the magnetic properties of columnar basalts from Bombay. Although, unlike the Giant's Causeway, little geological investigation has ever been made of these columns they are known to be hexagonal prisms of coarse-grained basalt about three feet across and up to more than 100 feet in height. No mineralogical variations from the centres to the edges are apparent in

either thin or polished section, yet hysteresis loops in a field of 1,500 oersteds show that coercive force increases from the edge to the centre both at 25° C and -190° C. A similar variation of coercive force is found in samples previously heated to above their Curie points, although in each case the coercive force is significantly higher than in the corresponding virgin sample. Changes in the magnetic state clearly take place on heating; and curves of low field susceptibility against temperature show that these changes depend on the position of the relevant sample within a column.

Because in most cases the coercive force and saturation magnetization of virgin samples do not depend on temperature between 25° C and -190° C, Radhakrishnamurty and his colleagues conclude that the operative magnetic mineral is neither magnetite nor titanomagnetite. On the other hand, X-ray diffraction studies indicate the magnetic mineral to be "akin to magnetite". For the heated samples the hysteresis loops indicate the presence of magnetite (mostly) towards the edges of the columns but maghemite towards the centres.

These data, together with hysteresis loop comparisons with synthetic magnetites and maghemites, lead Radhakrishnamurty *et al.* to believe that the operative magnetic minerals in the virgin basaltic columns are intermediate phases in the magnetite-maghemite oxidation chain. To account for this the authors propose that although magnetite formed uniformly throughout the magma during initial cooling, and before columnar jointing, subsequent (radial) temperature gradients would lead to variations in the degree of oxidation within a column.

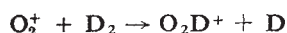
ION-MOLECULE REACTIONS

Precision Kinetics

from our Molecular Physics Correspondent

ONE of the most encouraging things about the present renaissance in chemical kinetics is the steady advance of both theory and experiment along lines which interconnect to a far greater degree than seemed possible ten years ago. While experimentalists are continually refining the accuracy with which the elementary reactive collision can be observed, theoreticians are beginning to grasp the nettle of calculating from quantum-mechanical principles the energy surfaces which must underlie any precise dynamical description of the sequence of events during a bimolecular encounter or a decomposition. One thing is important above all for this programme—the accumulation of reliable and precise data for reactions involving atoms and molecules with as few electrons as possible.

What is perhaps the most precise and thorough study ever made of a bimolecular reaction with small atoms has recently been completed at the Hahn-Meitner Institute in Berlin by Von G. Bosse, A. Ding and A. Hengelein (*Ber. Bunsenges.*, **75**, 413; 1971). The reaction concerned is the ion-molecule process



The accuracy achieved required a skillful combination of the most refined techniques for beam generation, definition and product detection, which, until recently, were more likely to be reserved for an atomic physics experiment. The O_2^+ ions could be generated in both the $^4\pi_u$ and $^2\pi_g$ electronic states; they were accelerated into a collision chamber containing deuterium, beyond which the scattered reaction products could be analysed for both angular distribution and energy using a quadrupole mass spectrometer with 'Channeltron' detectors. A variety of striking results emerged.

As a preliminary, Bosse *et al.* show that reaction of $^2\pi_g \text{O}_2^+$ sets in at a precise threshold energy (1.7 eV centre of mass) which corresponds closely to the independently calculated endothermicity of the reaction. This explicit demonstration of an activation energy — the fundamental experiment of chemical kinetics, in fact—would have been a sensational result in its own right not many years ago. The principal conclusions, however, are drawn from a series of energy-dependent scattering profiles obtained to quite unprecedented accuracy. Here the crucial feature is the presence or absence of isotropic scattering (centre of mass system) in the reactive-scattered beam of O_2D^+ . This is now accepted as a

sensitive indicator of the effective lifetime of a collision complex in a bimolecular encounter. Isotropic scattering arises where the lifetime is longer than or comparable with a rotation period; a "forward peak" in the scattering profile indicates a virtually instantaneous "stripping" mechanism for the process. By a peculiar quirk of the present reaction both possibilities can be observed in different energy ranges. With the $^2\pi_g \text{O}_2^+$ ion there is a long-lived complex at low incident energies (17 to 40 eV laboratory system) giving way at higher energies to a stripping mechanism in which the O_2^+ ion seems to extract one deuterium atom with virtually no momentum transfer to the other one. With O_2^+ in the $^4\pi_u$ state, however, there is no sign of a long-lived complex at any energy, a finding almost certainly connected with the strong repulsion caused by the parallel alignment of spins in the recoiling products. Much additional information is also extracted concerning interaction cross-sections, isotope effects with HD rather than D_2 , and the role of angular momentum. Significantly, almost all the heat of reaction in the exothermic $^4\pi_u$ reaction finds its way into translational energy of the fragments rather than into rotation.

There will certainly be much food for the theoretician in the results of

Hengelein's group and a strong stimulus to the search for other interesting reactions of comparable simplicity. At the same time, in setting new standards for the precision possible in ion-molecule studies, the results confirm that it is likely to be many years before anything like this degree of detail is possible in the results of experiments with neutral beams, notwithstanding the great advances recently made with these.

Although on the theoretical side enormous difficulties remain before a reaction, even of this simplicity, can be treated *ab initio*, there is still a great deal which can be learned by semi-empirical and computer simulation methods. One of the most striking aspects of the present move towards fundamentals is the shift which has occurred over the years in the use of the term mechanism, particularly so far as bimolecular gas reactions are concerned. No longer does this denote simply the gross particulars of intermediate stages which can be written out in chemical formulae; the term has increasingly taken on the meaning of collision mechanism; that is to say, a reference to the subtleties of the collision complex itself, its formation, lifetime and mode of decay, the arrangement of energy in its different degrees of freedom. The elucidation of the

Origin of Cosmic Rays

ALTHOUGH it is almost sixty years since Hess established the existence of cosmic rays the question of what fraction of the radiation, if any, comes from outside the galaxy is still unresolved. The Sun can on occasion produce charged particles with individual energies of up to 10^{10} eV. This energy overlaps the lower end of the cosmic ray energy spectrum in the region where most of the total energy resides, but the total output of this form of solar energy is very low and even if all other stars were as productive the observed cosmic ray energy density cannot be accounted for in this way. Because of this it is current fashion to think in terms of super novae explosions or pulsars as the principal generators of cosmic rays.

At the other end of the spectrum cosmic ray energies seem to go as high as 10^{19} to 10^{20} eV, if the interpretation of the large air showers is to be believed, and it has been customary to invoke an extra-galactic source for these super high energy particles because of the difficulty in finding sources with sufficiently high magnetic fields to accelerate them and because the interstellar magnetic fields are too weak to contain them within the galaxy.

Up to a few months ago the available picture of the general shape of the cos-

mic ray energy spectrum lent credence to a mixed galactic/metagalactic origin for the particles, but recent analyses of data from the large air shower array at Haverah Park have shown that the apparent decrease in slope of the spectrum above $\sim 10^{17}$ eV which was observed in earlier work at Volcano Ranch is almost certainly illusory. This change in slope had been attributed to a metagalactic cosmic ray flux.

In next Monday's *Nature Physical Science* F. W. Stecker re-examines the question of cosmic ray origin in the light of these results and of the interaction that should take place between ultra high energy metagalactic cosmic rays and the photons of the 2.7 K black-body radiation field. This interaction should lead to an upper energy limit to the cosmic ray spectrum and to a universal gamma-ray flux. Stecker considers several alternative cosmic ray models and concludes that the new spectral shape and the established upper limit to the gamma-ray flux are best explained in terms of a purely galactic origin for cosmic rays of even the highest energy. He offers only two alternatives; either the energy of air showers with $E \gtrsim 6 \times 10^{19}$ eV has been overestimated or there is no universal black-body radiation.

laws governing these details seems likely, not merely to provide an interesting chapter in chemical rate theory, but also to give firmer grounds for a claim that chemical reactive scattering is a subject worthy of the kind of attention which theoretical physicists have hitherto reserved for atomic and nuclear phenomena.

CANNABIS

Chemistry and Biology

from a Correspondent

LAST week (October 26 to 28) the Swedish Academy of Pharmaceutical Sciences sponsored a symposium on the chemistry and biological activity of cannabis which was held in the Foresta Hotel on the island of Lidingö, near Stockholm. The wealth of detail presented in the thirty-five contributions left no doubt that very significant advances in knowledge have been made since a somewhat similar conference was held two years ago (*The Botany and Chemistry of Cannabis*, edit. by C. R. B. Joyce and S. H. Curry; Churchill, London, 1970).

Work on the metabolism of the active tetrahydrocannabinol (THC) is now well advanced. Shortly after administration this highly insoluble substance is metabolized to the more soluble 7-OH, 6,7 dihydroxy and even more soluble acidic derivatives and several routes to the synthesis of these compounds and their radioactive labelling are now known (R. Mechoulam; J. L. G. Nilsson; T. Petrizilka). The THC seems to be fixed to some of the plasma lipoproteins (H. A. Klausner; M. Widman) and to be rapidly transferred to the liver, spleen and the cortex of the adrenals (J. I. Heikkilä; Ryrfeldt J. Schou). Microsomal oxidation produces the more polar metabolites and they, and unchanged THC, are found in brain tissue shortly after administration (S. Agurell; S. Burstein; E. W. Gill). Correlation of concentrations in the brain with behavioural effects in small animals, primates and man has been established (M. E. Wall; M. Willinsky; W. M. McIsaac; E. A. Carlini; J. Hrbek) although it is still not certain whether THC or its metabolites are the active substance (W. D. M. Paton, who also pointed out the interesting connexion between fat soluble anaesthetics and the fat soluble THC).

A second impression was of the scientific complexity of the cannabis problem. The plant itself is a very plastic species with a large variation in the amounts of THC produced (J. W. Fairbairn). Apart from THC, another thirty related cannabinoids have been characterized and some of these may be active (F. W. H. M. Merkus; T. B. Vree) or may modify the total activity; for

instance, cannabidiol (CBD) prolongs phenobarbitone sleeping time in mice (W. D. M. Paton). But P. Waser's suggestion that CBD is converted to THC on smoking was not generally accepted. Reports on the amount of THC surviving the smoking process gave results varying from 20 to 80 per cent, so that it was difficult to know whether a 5 mg, 10 mg or 20 mg THC content of a reefer would produce a "mind-rocking experience" or not. Even the nomenclature is confusing; sixteen contributions used the benzpyran system of numbering and thirteen contributions the terpenoid, so that one had continually to remember that Δ^1 and Δ^9 , or 7-OH and 11-OH, were the same compounds. Steps are being taken to rectify this situation.

O. J. Braenden (Division of Narcotic Drugs, UN, Geneva) and M. C. Braude (National Institute of Mental Health, Rockville) described their ambitious programmes to coordinate effort and reduce overlap and confusion as much as possible.

A third important topic discussed by a panel, with the press present, was whether cannabis is harmful to health. Although definitive answers are not yet possible, it was interesting to note that, in the light of recent knowledge, nearly all the experts gave the impression they were against liberalization of use. The serious possibilities were raised of

teratogenicity, tachycardia (especially if main-lining ever started), brain damage, accumulation in body fat, interference with microsomal enzymes (and therefore unknown effects on other drugs being taken for medicinal purposes), and carcinogenicity because deep inhalation is necessary for the full effect of a reefer. More general effects are a motivation leading to lack of drive and "dropping out", although N. E. Zinberg stated he had not noticed this markedly after a study of marihuana use in Vietnam. Unpleasant psychotic effects are also frequently reported and experimental work shows a slowing down of reaction time and inability to estimate time accurately; these effects can be serious when driving a car. Sir Harry Greenfield (International Narcotics Control Board) also pointed out that countries with a long history of cannabis use (for example, India, Egypt) are the most insistent on strict legal control.

A final impression gained was the hope that useful therapeutic substances may yet emerge and R. K. Razdan's work on crystalline water soluble derivatives of THC with interesting pharmacological properties may point the way. Abstracts only of each contribution will be published in *Acta Pharmaceutica Suecica*. Addresses of the speakers mentioned in this report may be obtained from *Nature* office.

Regulating the Initiation of Translation

THE notion that initiation factors in *Escherichia coli*, by regulating the binding of ribosomes to specific "start translating" signals in messenger RNAs, regulate the expression of particular genes at the level of protein synthesis, receives further support in next Wednesday's *Nature New Biology*. Berissi, Graner and Revel, who have studied the effect of initiation factors F2 and F3 on the binding of *E. coli* ribosomes to the RNA of bacteriophage MS2, a close relative of R17, conclude that factor F3 selectively promotes the initiation of translation of the MS2 coat protein cistron.

The binding of ribosomes to MS2 RNA in its native configuration depends on the presence of two initiation factors, F2 and F3. If, however, the MS2 RNA is partially denatured by exposure to dilute formaldehyde, a procedure developed by Lodish, ribosomes will bind to the RNA in the absence of factor F3 although factor F2 is still required. This finding provided Berissi *et al.* with an opportunity to ask whether or not F3 is capable of promoting the specific attachment of ribosomes to one or more of the initiation signals on MS2 RNA. In essence all they had to do was compare the ratio of the number of sites on partially denatured MS2 RNA bound to and protected by ribosomes in the presence of F2 alone or F2 and F3.

The results of such experiments proved to be all that anybody could hope for. With factor F2 alone the ribosomes bind to the initiation sites of the coat protein, RNA replicase and maturation protein in the ratio of 1:2:1 but when factor F3 is also present, although the total number of ribosomes bound does not alter significantly, the ratio is shifted to 1:0.5:0.14. In other words factor F3 specifically promotes the recognition of and binding to the initiation signal at the beginning of the coat protein cistron at the expense of the other two cistrons; factor F3 promotes the expression of the coat protein cistron.

Berissi *et al.* have started to look for other F3 factors which might specifically promote the translation of other cistrons or sets of cistrons, for the idea that gene expression is regulated in part by a battery of different F3 factors is obviously most attractive. So far they have discovered one other F3 factor, called F3B4 to differentiate it from F3B2 which promotes the recognition of the MS2 coat protein cistron. F3B4 does not stimulate the attachment of ribosomes to MS2 RNA but it does stimulate translation of phage T4 messenger RNA; it will be no surprise if the list of specific F3 factors rapidly lengthens in the near future.

SELFASSEMBLY

Tricks with Ribosomes

from our Molecular Biology Correspondent

SINCE Nomura and his colleagues achieved the small miracle of mixing 16S RNA with its complement of some twenty ribosomal proteins to give active *Escherichia coli* 30S subunits, strenuous and hitherto unsuccessful attempts to reassemble the large subunit of the same species have been made in many laboratories. True, Nomura's group succeeded with 50S ribosomes from the thermophilic organism, *Bacillus stearothermophilus*, so that the principle has been in no doubt. Now, however, Maruta, Tsuchiya and Mizuno (*J. Mol. Biol.*, **61**, 123; 1971) have found the conditions for making active *E. coli* 50S subunits from their constituents, and more, regenerating the small and large subunit simultaneously in a single mixture of the three ribosomal RNA species and all the proteins—a process which may be compared to assembling a watch by putting all the parts in a bag and shaking.

The trick, so far as the 50S subunit is concerned, is to avoid exposure of the proteins to the solvents that are normally used for extraction and dispersion. Instead they are freed of RNA by treatment with nuclease. The native ribosomes are very resistant towards nucleases, but after partial unfolding in a medium containing molar ammonium chloride, the RNA becomes labile. When treated with the endogenous *E. coli* ribonuclease II, therefore, the RNA is hydrolysed to oligonucleotides, and the proteins are left, mostly as a precipitate, which will dissolve in a concentrated buffer solution. This is the protein preparation used in the reconstitution experiments, for if any attempt is made to remove nucleotide material by dialysis, no ribosomes can be regenerated. Evidently, therefore, some of the 50S ribosomal proteins are easily converted into a state from which specific interaction with the other ribosomal constituents becomes impossible. Bovine serum albumin is also included in the mixture as an obscurely beneficial component.

The reassembly reaction has a number of remarkable features. As with *B. stearothermophilus* ribosomes, the functional 50S subunit is not formed unless 30S subunits are present, or alternatively, as Maruta *et al.* now find, the mixture of the proteins and RNA of the 30S subunit. Moreover when only the proteins originating from either the 50S or 30S particle are labelled, all the label reappears in the right place after reassembly. That is to say none of the proteins from either subunit are captured by the other subunit, in spite of their basicity and the stupefying complexity of the system. The resulting

ribosomes are active in poly U and viral RNA-dependent polypeptide synthesis. The 5S RNA which resides in the large subunit is indispensable for activity. It may be added separately, as a final step in the reconstitution process.

This last effect—the reversible release of 5S RNA from the 50S subunits—has been studied in other laboratories. Gormly, Yang and Horowitz (*Biochim. Biophys. Acta*, **247**, 80; 1971) have also used concentrated ammonium chloride at low magnesium concentrations to bring about a partial relaxation of the subunit to a more slowly sedimenting state. Liberated with the 5S RNA under these conditions are several ribosomal proteins, four species being completely and another three partially dissociated. On returning the ribosomes to their usual magnesium concentration, the 5S RNA is taken up, and folded subunits again appear. This process, however, also required the pre-

sence of the dissociated protein fraction—a conclusion apparently at odds with a report last year by Reynier and Monier. Unfortunately the restored ribosomes appeared not to be biologically active.

Gray and Monier (*FEBS Lett.*, **18**, 145; 1971) have tried another approach to identifying the ribosomal proteins directly associated with 5S RNA. They incubate 23S and 5S RNA with fractions of 50S ribosomal proteins and detect the formation of complexes by the membrane filtration method. A magnesium-dependent stable complex is indeed formed with one column fraction of 50S proteins. This complex can be isolated by sucrose gradient sedimentation, and when the proteins are analysed by gel electrophoresis three major and two minor zones can be resolved. One of the former is associated with 23S RNA even in the absence of 5S.

Infrared and the Black-body Background

SINCE the discovery by Penzias and Wilson (*Astrophys. J.*, **142**, 419; 1965) of 7 cm radio noise, thought to be remnant cosmological radiation with a black-body temperature of about 2.7 K, much attention has been paid to measuring the background radiation of the sky at wavelengths from the near infrared out to the radio region. Measurements which verify the possible existence of the background radiation have been made on the long wavelength side of the black-body peak, predicted to be at about 1.5 mm, but observations near the peak and at shorter wavelengths are not possible from the ground because of atmospheric absorption.

In recent years rockets have been used for investigating the sky background in the millimetre, sub-millimetre and infrared spectral regions from above the atmosphere. Two contributions on this topic appear in next Monday's *Nature Physical Science* and present conflicting measurements of the far-infrared background levels. D. P. McNutt, K. Shivanandan and P. D. Feldman report results of a recent Naval Research Laboratory flight in which they measured sky background in the 10 to 30 μm , 100 μm and 280 μm regions. A. G. Blair reports on rocket measurements obtained by the Los Alamos group in the 65 to 70 μm region.

The NRL experiment was launched on a Black Brandt VB rocket from Wallops Island on February 24, 1971, at 2013 EST and data were obtained between altitudes of 130 km and 275 km over a time period of 135 s. The photometer was cooled to a temperature of 2.8 K and the intensity calibration was estimated to be accurate to within a factor of two. Results indicated that at zenith angles less than 20°, scattered

earthshine was unimportant, and the signal levels were interpreted in terms of a true background 100 μm radiance of $1.4 \times 10^{-9} \text{ W cm}^{-2} \text{ sr}^{-1}$ and a 280 μm radiance of $2.9 \times 10^{-9} \text{ W cm}^{-2} \text{ sr}^{-1}$.

The Los Alamos experiment was launched from Kauai Test Range on May 29, 1971, at 0048 HST and carried a radiometer cooled with liquid helium to measure background fluxes in the spectral region 65 to 170 μm and 0.8 to 6.0 mm. The 0.8 to 6.0 mm results are not inconsistent with the proposed background 2.7 K black-body cosmic radiation. These results are discussed in a previous publication (*Phys. Rev. Lett.*, **27**, 1154; 1971). In the 65 to 170 μm region, Blair puts an upper limit of $1.2 \times 10^{-10} \text{ W cm}^{-2} \text{ sr}^{-1}$ on the 100 μm radiance. This figure is consistent with previous results obtained by both the NRL group (*Science*, **167**, 1277; 1970) and the Cornell group (*Nature*, **281**, 375; 1971) but is more than an order of magnitude less than the current results of McNutt *et al.*

In looking for reasons to explain this large difference, McNutt *et al.* discard the possibility that they are detecting ionospheric radiation. Summarizing all rocket data available for the 100 μm and 280 μm regions, they conclude that those flights near local midnight show comparable low radiance levels whereas the earlier Cornell experiment (*Science*, **164**, 1271; 1969) and their current results—both recorded near astronomical twilight—are significantly higher. They suggest the possibility of a contribution from the outer magnetosphere, or near-Earth interplanetary space, which could be subject to a diurnal variability. They reject, however, the likelihood of a correlation between radiance and geomagnetic index K_p .

YEAST

Control of Budding

from our Microbiology Correspondent

WITH so much being written these days on the subject of morphogenesis and its biochemical foundations it is refreshing to come across a piece of work in which cellular differentiation has been resolved in some detail at the molecular level. Dr Enrico Cabib and his colleagues at the National Institutes of Health in Bethesda have been following a very simple morphogenetic event, that of budding in yeasts. Their latest findings (Cabib and Farkas, *Proc. US Nat. Acad. Sci.*, **68**, 2052; 1971) bring together the details of a chitin synthesizing system which is responsible for initiating septum formation between the mother and daughter cells. The specificity both of timing and localizing this event seems to be produced by conversion of a chitin synthetase zymogen to the active enzyme by an activating factor (AF).

Earlier this year, Cabib and Bowers (*J. Biol. Chem.*, **246**, 157; 1971) had confirmed previous reports that chitin is concentrated in a disk-like plug from which the bud has detached. They have now shown that chitin synthesis occurs in a stepwise fashion in synchronized populations of *Saccharomyces carlsbergensis*. Similarly the chitin synthetase of *Saccharomyces* species which was described as a particulate enzyme (Keller and Cabib, *J. Biol. Chem.*, **246**, 160; 1971) is revealed to be largely in an inactive or zymogen form which can be activated about 15-fold by treatment with trypsin. The endogenous AF can be recovered in high-speed supernatants of the sonicated enzyme preparations. Although the details of the AF have not been elucidated, it probably catalyses a specific proteolysis of the zymogen. Cabib believes that the enzyme is firmly bound to a particulate cell fraction whereas AF is enclosed in more fragile vesicles.

The nature of the synthesizing system is still more complex. A heat stable protein was discovered in the cytoplasm which was thought to be an allosteric inhibitor of the enzyme (Cabib and Keller, *J. Biol. Chem.*, **246**, 167; 1971). But further work has confirmed that the inhibitor interacts with AF and not with the enzyme *per se*.

In order to explain the triggering of chitin synthesis at a precise time and site, Cabib and Farkas offer the following hypothesis. Because chitin synthetase is largely in a zymogen state and the amount of it in the cell is surprisingly constant, it is presumed to be uniformly distributed in some structural component of the cell, most probably the plasma membrane. Following bud formation, AF-containing vesicles might fuse with the plasma membrane at the site of septation resulting in enzyme activation of

chitin synthesis. Indeed, the presence of vesicular material at bud sites has been observed several times in yeasts. The role of the inhibitor is more enigmatic. One possibility is that it may serve as a safety device to immobilize AF that might be released into the cytoplasm and thereby prevent any indiscriminate enzyme activation and subsequent chitin formation. Experimental testing of this elegant model doubtless will be made in the near future and news of its veracity and generality will be eagerly awaited.

MICROSCOPY

Cryoultramicrotomy

from a Correspondent

A MEETING and workshop on cryoultramicrotomy was held in Paris on October 18 and 19 and was the second meeting on specialized techniques in microscopy organized jointly by the Royal Microscopical Society and the Société Française de Microscopie Electronique.

Dr W. Bernhard (Institut de Recherches Scientifique sur le Cancer, Villejuif) opened the session by reviewing the problems posed by cryoultramicrotomy, and showed that by carefully applying the technique to material which had been lightly fixed it was now possible to obtain morphological information from specimens equal to that obtained by more conventional techniques of embedding and thin sectioning. This excellent introduction to the meeting was followed by a series of contributions by commercial representatives on the physical principles of cryoultramicrotomes. No major advances in instrumentation were described, but all the speakers in this session stressed the importance of accurate temperature control of both the knife and specimen, and the necessity of a dry atmosphere in the cutting area.

The remainder of the first day was taken up by descriptions of some biological applications of the cryoultramicrotome. Dr L. Seveus (LKB, Stockholm) and Dr G. Werner (Saarlandes University) showed that fixed material, frozen, thin sectioned and then dried at low temperature, can give the same type of image obtained by more conventional means, although membranes can only be seen in negative contrast. Organelles such as mitochondria, although recognizable in unfixed material, rarely show internal membranes. Dr T. Appleton (University of Cambridge) gave several useful hints for the handling of frozen sections, and for drying the sections at low temperatures. He also showed that ultracellular membranes in unfixed material seem to appear as an array of linear dots, and said that the interpretation of morphological data obtained by cryoultra-

microtomy should not be based solely on the usual appearance of these structures in the electron microscope. Dr L. Paavola and Professor A. K. Christenson (Temple University) showed how necessary it is to work with unfixed material in studies of steroid synthesis in mammalian tissue.

On the second day, Dr S. Hodson and Dr J. Marshall (Institute of Ophthalmology, London) showed that even if sectioning is carried out at -180°C there is still likely to be some danger of surface melting of the specimen. Their studies showed that although this melting is considerably diminished in very thin section, it might seriously jeopardize high resolution localization of diffusible substances. The session continued with a paper on sectioning single cells and a discussion on whether it is really necessary to encapsulate the specimens before freezing. Dr A. Viron (Laboratoire de Biologie de Végétale, Orsay) and Dr S. Halpern (Institut de Recherches Scientifique sur le Cancer, Villejuif) described some results following cryoultramicrotomy of plant material, and it became clear that the watery vacuole of mature plant cells still presents a considerable barrier to successful cryo-sectioning of plant tissues. There then followed an exhaustive round table discussion which included contributions by Professor H. Moor (Technische Hochschule, Zurich), Dr P. Echlin (University of Cambridge) and Dr M. Grund (Reichert, Berlin) on some of the theoretical problems associated with rapid freezing. It was shown that the present techniques preserve adequately only the surface layers of specimens unless the samples are thoroughly soaked in cryoprotective agents. In many future applications of cryoultramicrotomy the use of fixatives and anti-freeze agents may not be practicable, and several new techniques were discussed including the high pressure method proposed by Professor Moor.

The afternoon session dealt with the application of cytochemical method and autoradiography to cryoultramicrotome sections. Dr Appleton showed that it was possible to localize by X-ray microanalysis ions and electrolytes in frozen dried sections, and Dr R. Simard (University of Sherbrooke) demonstrated the rapid loss from the tissue of diffusible substrates in material which had been fixed before freezing and sectioning.

In summing up this most stimulating meeting, Dr Bernhard agreed that the cryomicrotome has proved itself capable of providing morphological information, but said that its use should now be directed to providing thin sections of undisturbed biological tissue for analysis by the sophisticated techniques of histochemistry, autoradiography, immunochemistry and X-ray microanalysis.

Conflicts of Loyalty in Science

Although there is a traditional view that the chief duty of scientists is to the scientific community, their employment by government, industry or even universities may frequently impose other loyalties. At a symposium held on September 7, 1971, at the annual meeting in Swansea of the British Association for the Advancement of Science, an attempt was made to help to define the line that must be drawn between one loyalty and another. This article brings together the contributions to the symposium by Dr K. Mellanby, Mr Terence Price and Dr J. R. Ravetz.

K. MELLANBY

Monks Wood Experimental Station, Abbots Ripton, Huntingdon

BEFORE considering the scientist's responsibilities, we need to know a little more about him. Is there such a thing as "a scientist", someone who differs from the rest of humanity? Is the term now more or less obsolete and can we explain the difficulties of the British Association for the Advancement of Science by saying that "science" is no longer the distinct and meaningful term it once was? I think we must consider this carefully, because the layman still thinks of a scientist as a polymath, a person who can speak expertly on any scientific subject. Unfortunately some so-called scientists also make the same mistake, and pretend to give an informed and scientific judgment on subjects in which they themselves are laymen. They are disloyal to science.

To some, a scientist (particularly a research worker) is a glamorous figure, making epoch-making discoveries at frequent intervals. His work is considered important. If he works on the right subject, he will benefit mankind immeasurably, but if he studies the wrong topic, he will do untold harm. This picture is, of course, generally false. Most scientific research may add slightly to the body of knowledge, but most of it has almost no practical significance. It adds a few bricks to the edifice of knowledge, or a sliver of mortar. Most scientists are, in fact, profoundly unimportant.

This unimportance is accentuated by the fact that many scientists, even in universities where they have a considerable degree of freedom in the choice of their research subjects, seem to have a genius for selecting the trivial and avoiding the significant. Those who control research policy and those who direct other scientists are equally inept. But spotting the significant topic is not an easy matter and the elitist, academic approach to research—to work on a subject which may seem interesting and to damn its practical importance—may sometimes produce the best and most valuable results, even results useful to the technologist.

Thus last year, at the meeting of the British Association, Dame Honor Fell gave an outstanding presidential address to section D (zoology). She showed how practical results of great medical importance arose from the work of scientists working in different laboratories over a period of almost a hundred years; none of the work was aimed at its ultimate target.

The seemingly important subject may also disappoint. Until

recently biologists have been impressed by the immense significance to mankind of molecular biology, and participants in this research have, deservedly, received a galaxy of Nobel laureateships. Now Sir Macfarlane Burnet states, with some authority, that all this brilliant work has made no contribution of any significance to medicine; he is even convinced that it never will.

There is also an interesting situation in ecology. We have been told that real progress will come from two directions, ecological energetics and computer-aided systems analysis. In the long run this may be true, but I have my doubts; I think that the practical value of this work is limited. At the same time we constantly hear that field studies are "mere natural history", a waste of time and energy, an unnecessary muddying of our ecological gum boots. We now know that just these studies, this natural history, has provided us with the most delicate tool for the early recognition of environmental pollution—and it is no accident that most of the members of the Royal Commission on Environmental Pollution are biologists, including at least three with extensive experience of just this sort of ecological field work.

Thus it appears that, although it is the responsibility of the scientist to wish to work in the field where his results will be of most value to science and mankind, the selection of this field may not be easy. The results are seldom those expected at the start of the work—if they were, then the work would not be really necessary! We should not, however, scorn the short-term *ad hoc* work, clearly intended to solve a practical problem. It seldom does so, but in the hands of good research workers, it often reveals unexpected and fundamental truths.

Scientists today may play an important part in giving advice to governments or to the public; this they have a duty to do. Unfortunately others cannot always distinguish the genuine from the bogus. A scientist may be the unique authority in his own speciality, but he is also a layman outside that field. If he allows himself to be considered an expert when he is not, he is a fraud and disloyal to science as a whole. We often come across these bogus experts nowadays, particularly in the realms of ecology, of pollution, and of pesticides. Let them remember that they are not polymaths, and keep their allegedly expert comments to their own restricted speciality. This does

not mean that a scientist cannot speak out on all sorts of other matters, political and sociological, but he does this as an ordinary citizen and not as any sort of expert.

Knowledge is universal, and scientists have a duty to make their findings available to all. I would accept that someone employed in industry must, for a time, keep technical details of industrial processes secret and those who object are objecting to our capitalist system, not to something fundamental to science. I also accept that someone working in a military establishment must abide by the rules he accepts when he enters that sort of employment. Many may also object to this—the objection here is a legitimate political one, it is the advocacy of pacifism, and again the objection is not fundamentally a scientific one. With these possible exceptions, I believe that it is the duty of a scientist to make his work known and to give his expert advice whenever possible. Unfortunately there are cases where he may be prevented from so doing. A scientific civil servant does accept some limitations on his liberty, but these should be enforced as little as possible.

I believe our authorities have quite a good record in this connexion, though I have, as editor of the scientific journal *Environmental Pollution*, known scientists in government laboratories to be forbidden to publish information, which cannot possibly be considered as affecting national security, for the administrative convenience of their minister. What is particularly objectionable is that the minister himself may know nothing about the prohibition, made in his name by some comparatively junior civil servant.

A scientist in a research council must never be so muzzled. Since the research councils were put under the Department of Education and Science, there has been a tendency for scientists to be told they must behave like civil servants and must not say or do anything which might "embarrass their minister". This is dangerous, and could lead to a situation where the only real experts, not the bogus ones who so often hit the headlines, are prevented from speaking—for in some subjects all the principal workers are employed in some way by government.

TERENCE PRICE

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I HAVE been asked to say something about conflicts of loyalty as they might concern someone with a broadly scientific or technical background who works at a fairly senior level for the government. In one sense this is a relatively easy task, because no one can reasonably ask me to resolve such conflicts once and for all. The point is that the work of government is precisely about conflict, and to assume that in a better-ordered world these conflicts might in some way be avoided is to ignore the obvious truth—that if any issues were so easily resolved they would have been settled lower down, without reaching the government level at all. Government cannot avoid dealing with that residue which defies orderly treatment. And because there is this conflict of policies, and because—fortunately—it is still men and not machines who engage in the final arguments, we must expect a similar conflict of loyalties to be only a step away.

The first point I would make is that many kinds of people, many professions and many interests necessarily have to contribute to these discussions. Science is only one voice amongst many. But it has one very important claim to a place at the top table: it is by far the largest inducer of change that the world has ever known.

This, of course, does not always make for the easiest professional relationships between scientists and their non-scientific colleagues. Science in a sense progresses blindly. It does only what it can. In the process it is continually creating problems, and there is nothing in the scientific method that guarantees that it will also provide solutions. Nothing could be further from the precepts of tidy administration. The man in Whitehall may not always know best (and in any case he is much too experienced to make such a claim) but he does know instinctively that some brake must be set on the rate of change if all is not to dissolve in chaos. His experience leads him to distrust men who claim that this or that project will, at a stroke, bypass some existing difficulty and lead us automatically into a better world. He sets more store by the words of Francis Bacon: "It were good therefore that men in their innovations would follow the example of time itself, which indeed innovateth greatly, but quietly, and by degrees scarce to be perceived; for otherwise, he that is hurt takes it for a wrong, and imputeth it to the author". And again: "Those things which have long gone together are confederate within

themselves, whereas new things piece not so well". We are not dealing with a new phenomenon. It is only the scale that has changed.

But in changing the scale we have created a new source of conflict between science (and I am using the word to include technology) and all the other claimants on national resources. Generally speaking—as Sir Alec Cairncross stressed at the beginning of this conference—the growth of science has not, in practice, been matched by any very convincing relevance to the needs of the national economy, nor by any explicit commitment to social objectives. Our promises as scientists were listened to with attention during the fifties, and if we had got things right this might still have been the case. But too much went wrong with atomic energy policy, and a king's ransom was squandered on cancelled aircraft. We never had it so good, and we shall never be allowed to have it so good again. If this leads us—indeed forces us—to be more objective about our own personal projects, it will, I think, be no bad thing. In the long run it may well be better to have doubts before the event about (say) the noise pattern which a city centre VTOL airport would create, than to pretend that its impact would be minimal.

But such doubts will not make running a large organization any easier. Large projects, like the VTOL city-centre aircraft of my example, can only come together successfully and on time if there is a unity of purpose in the execution, and an ability to enthuse the team with a belief in the rightness of their task. The Americans talk of "missions"—a well-chosen word with exactly the right quality to fire the zealot hidden in every man. But sophisticated doubts about mission objectives can create very personal conflicts for the mission leaders, particularly if they are also men who operate at a high level in the national context. In such a capacity they have to make judgments about the overall national good. But their entitlement to make such judgments springs from their position as spokesmen for large technical organizations, in which role they are expected to prevail in argument and to bring home the bacon in the shape of a fat allocation of resources. Here is a potential conflict which is usually inescapable. Not everyone finds it easy to resolve. Indeed, not everyone makes the attempt. The much vaunted objectivity or self-discipline of science applies, in fact, only to the actual process of observing

or interpreting natural phenomena. There is not much evidence to suggest that this objectivity spills over into the wider social context.

In practice an administration defends itself against project leaders' more extravagant claims—not always very successfully, it is true—by taking some of these poachers and turning them into gamekeepers. Hence those shadowy teams of “neutrals” in places like the Cabinet Office. The conflicts of a neutral are more subtle. Lacking the support staff who would be needed to work up a view in the same detail as those who are putting forward a programme for expenditure, he usually has to make do with scanty information, and relies a good deal on hunches. He runs the risk of falling into the danger of pretending to a degree of detailed knowledge which he does not possess. Or he may become a persistent critic: all policies can be faulted, and it is easier to destroy than rebuild. The persistent critic eventually wears thin the patience of his colleagues, like a compulsive litigant. By squandering his resources he paralyses his ability to intervene on the really important issues. Most men are alive to this danger, and do not chance their arm too frequently. But there is then the possibility that they will be led into keeping silence at a time when it is necessary to speak out. “Don't rock the boat” can be a very effective curb.

When to break with established policy and take one's stand is indeed a terribly hard thing to judge. Once the move has been made it is irreversible. It is unwise to be wrong—particularly if, as can happen, you find yourself wishing to challenge the policies of some other sector of the organization. It is all too easy to be deterred by that other war-cry: “No influence with responsibility”. Nevertheless challenges are made—though it is as well for the challenger to be equipped with adequate standing or adroitness.

At this point I can imagine someone saying—and indeed this was said earlier in this conference—that things would be so much easier, and there would be so many fewer conflicts, if only the government allowed its professional staffs to carry out their analyses of social and economic return in greater depth, and in more explicitly numerical form. To which the only possible answer is fiddlesticks. I have seen at first hand the workings of a large government group devoted to operational analysis. It tackled some largish issues and, I believe, made a useful contribution. But this did not automatically lead to a Utopia in which there were no conflicts—it simply shifted the point of contention to a different part of the decision chain. Herman Bondi once said: “If I find one of my students who has reached an answer with which I disagree, I never look at his mathematics. His arithmetic is always right. I look at the assumptions which precede equation one.”

It does not take anyone who has suffered from an unwelcome conclusion of an operational analysis study—and has come near to losing his own project as a result—to learn this lesson: he ripostes by attacking the assumptions. Moreover, this kind of analysis is a game that two can play, and once a fashion for decision by analysis has developed it is not too difficult for a skilful staff to decide on the desired outcome, and then to construct an analysis which will point in that direction. Nor is this necessarily wrong. Debate is a good thing and out of it may, perhaps, come truth. My point is that it is naive to hope that by any purely technical approach these conflicts and debates can be avoided. They cannot, because they are fundamental. And in any case numbers can be a terrible straitjacket. As Denis Healey once remarked: “Don't just give me facts that can be expressed in numbers. I also want facts that can only be expressed in words.”

Anyone who has read Parkinson, or Snow—or even Solzhentyn—will recognize these conflicts as those of any organization man. And you may wonder that I give them so much prominence, where others might have preferred a discussion of more meaty issues, like biological warfare. The fact is that

I have not, in my own experience, found that these have led to a personal conflict of loyalties, whereas the others are there with you (and all other organization men) all the time, each time you enter your office.

I can, of course, well imagine that the conflicts posed by Porton or Aldermaston are real enough for those who work there; but I was fortunate in having to deal with such issues only at several removes, and I have no quarrel with the way in which I was allowed to work out my own thinking. Indeed, in relation to the political and military problems posed by the existence of nuclear weapons, I can only regard the attitudes of my own immediate colleagues as enlightened. One of the problems was the effect of the development of atomic energy on disarmament policy. The point was taken early on that there were limitations on the extent to which fissile material could be tracked down, and thus on the degree to which it would be safe to reduce both nuclear and non-nuclear armaments. Total nuclear disarmament was therefore a non-starter. But some attitude had to be taken by the government, and we were privately encouraged to clear our minds on what, if anything, might still be possible. We took part in the disarmament conversations at London and Geneva, and were encouraged to go if we wished as observers to Pugwash, or to participate in private meetings of bodies like the Institute of Strategic Studies. There was no intellectual conflict here—it was the problems that were difficult. The more one became acquainted with the issues, the less one felt able to share the certainty of the Aldermaston marchers, admirable though they were as people. And yet they were not wholly without influence: it may have been partly due to their conviction that something ought to be done that it was possible to have a serious, and on the whole reasonably convincing, discussion within Whitehall. Whatever the reasons, I personally never felt myself under pressure to subscribe to a doctrine in which I did not believe.

What I did sometimes regret was the inability to communicate this feeling to the public at large. The inhibitions about publication, already mentioned by other speakers in this discussion, naturally loom very large in such a field. This stems to some extent, here and elsewhere, from the constitutional doctrine that only the minister is permitted to enunciate policy. One cannot help feeling, with government activities as widespread as they are today, that this doctrine is perhaps in need of some overhaul.

It may be relevant that the intellectually satisfying atmosphere that I am describing occurred during a period when the Ministry of Defence had at its head (under the minister) three very remarkable men—one of whom had only recently come in from outside the civil service. The place of irregulars in Whitehall is a favourite battle-ground, and I certainly do not wish to adopt a doctrinaire attitude. Some of the importations have not worked, and only rather exceptional men have learnt to take their place in such a complicated machine, and to be really effective. Nevertheless one could be forgiven for doubting whether a government service that was wholly inbred would always be capable of creating the atmosphere of intellectual stimulation that I was fortunate enough to experience. The irregular has an essential function to perform. And even for him it will not always be easy.

In case I seem to be straying too far from the subject, let me say that the link in my mind is the question of how we are to handle the really central issues. These are what tear men apart unless they are dealt with effectively. Anyone who has sat through the meetings of the British Association knows that problems are going to increase, in intensity and in number, as the human race learns to live in balance with the rest of this small planet. In the process, we shall have to develop a new basis for economics and a new orientation for technology. Even the moral basis for our policies may come increasingly into question. All this, to my mind, underlines the need for the changes that are now beginning to take place—too slowly,

perhaps—in the structure of the government service. If they mature, they should go some way towards minimizing the danger of inbreeding, and should avoid at least some of the conflicts which could occur if the government machine failed to keep up with change in the world outside.

I will end with three thoughts. First, there is the need to recognize the perennial nature of the conflicts which we face. Only the subject matter, and perhaps the pace, are new. The methods by which they will ultimately be resolved—with more or less elegance, depending on the participants and the luck of the draw—will be those on which the human race has always had to rely: argument, persuasion and decision. If scientists are dissatisfied with the way in which the great issues are tackled, by all means let them go and try their hands at doing

better—but only after due preparation. The requirements for success in the world of affairs, or (to use Lord Zuckerman's telling phrase) for effectiveness at the point of action, are what they always were—you can find all you need in the essays of Francis Bacon from whom I quoted earlier. Do not make the mistake of thinking that the sociology of a government department equates with that of a laboratory or a university. They have very little in common. Second, the institutions within which the conflicts are resolved are very relevant; they deserve the closest attention. Third, the quality of argument within the government machine is often encouragingly, even outstandingly, good. Some of the fears which exist might well be removed if the arguments could be made more easily available to the general public.

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I FEEL that I must challenge the assumptions on which our discussion is based. May I call your attention to the opening clause of the statement of the scope of the session: "Scientists are brought up to believe that their chief duty is to the scientific community . . .". I am sure that to the organizers of the session, this was obvious common sense. But we live in an age when common sense becomes obsolete with increasing speed, and the common sense of the social activity of science is no exception. For this statement is an assertion about a state of affairs among a particular social group: advanced students of science. As such, it may be true or it may be false; or it may be that it was true yesterday but will be false tomorrow. Whatever its degree of correspondence to the social reality of science, this can be determined only by a study of evidence concerning that social reality. And on balance the evidence indicates that it is no longer true.

I am not raising this objection merely to be difficult; there are two important points concerned with it. The first is that this statement belongs to a field of enquiry that can be called "the sociology of science". The field is small and fragmented; and it is possible that reflective scientists can offer more insights to it than those who approach science from the outside. On the other hand, its problems are not those of research science and, in this field as in any other, pitfalls abound for those who are overly confident in their common sense understanding of its phenomena and problems.

It is true that until recently sociologists of science accepted and reinforced the common sense view that neophyte scientists are inculcated with a sense of duty to their scientific community. But as soon as serious empirical studies began to be conducted, this common sense was exposed as a myth, at least as regards the situation today. Here I refer you to the writings of Box and Cotgrove, Ernest Rudd, Norman Ellis and Barry Barnes. So my first point is that scientists who engage in the laudable and necessary work of discussing the social problems of science would do well to remember that even when discussing themselves, as members of a group, they are amateurs.

The second point is more serious. For if, as I maintain, the common sense view about this important aspect of science is no longer true, then there is a two-fold consequence; the social activity of science has suffered an important change in recent times and the common sense of some leading scientists has not yet caught up with it. In that case, the discussion of "duties" and "loyalties" among the units of scientific manpower, or

QSEs as they were labelled not long ago, is only partially relevant to the social problems of science at the present time.

This is not to say that conflicts of loyalties are now insignificant for the life of science. They are there but I shall argue that the most important foci of conflict are no longer those around traditional professional groupings and roles. For these have become attenuated and, at the same time, some other, very deep problems have become recognized. I will try to identify these new conflicts of loyalty in terms of the new social character of science.

A clue to the change in science is provided by the term "the scientific community". The last word, much overworked nowadays, bears with it connotations of what the sociologists call *Gemeinschaft*: a group held together by stable, direct, interpersonal relationships. By the end of the past century, social philosophers recognized that this type of society was rapidly being extinguished in Europe and being supplanted by one they called *Gesellschaft* where the relationships are essentially impersonal and the ties are contractual and formal.

We have long been familiar with the distinction between "little science" and "big science" and it seems to me that the implied change in scale carries with it very deep consequences for the character of the social activity of science, along the lines of the change from *Gemeinschaft* to *Gesellschaft*. I have described elsewhere the difference as one between the "academic science" of the recent past, and the industrialized science" of the present. By industrialized I do not merely mean that science has come to be considered primarily as a factor in production when it is being planned. And the capital-intensive character of research makes inevitable a concentration of decision-making power and a differentiation of scientists into groups analogous to social classes, where the many are dependent on the decisions of the powerful few. Also the supposed economies of excellence of scale among the social units of production lead to a concentration of research, and even more of research training, in favoured large centres. These conditions are very different from the earlier state of largely independent individual scientist-craftsmen, each being able to accommodate only a few apprentices and being sufficiently small and poor a community to be bound by personal ties and governed by largely informal means.

With such a drastic change in the social character of scientific research, we must expect significant changes in its more subtle ideological aspects. To be brief, the graduating scientist finds

the best job he can; he does not join a profession and still less does he take up a vocation. This is my impression, based on talks with young scientists, and I am supported by scholarly social investigation. For this generation of recruits, conflicts of loyalties of the traditional sort are usually absent.

I can agree that the problems referred to in the statement of the scope of our session are real ones; I would only prefer to describe them as problems of responsibility. For the scientist working in a university, nominally in a "pure" field, they can be severe and, on occasion, destructive. For the university man's job includes several roles including that of teacher, social worker, administrator and researcher. We are all aware how the progress of his career within institutions performing these multiple functions is determined largely by his prowess as a researcher which is assessed by networks of colleagues that operate across and outside such institutions. The recent American experience of student revolts shows what happens when the conflicts inherent in that situation are not controlled. For there the great universities, or multi-versities, had degenerated into unstable collections of research baronies. Faced with crises affecting them as institutions, they were paralysed. To describe the cause of this as a conflict of loyalties is to miss the point entirely; for it was the total absence of loyalty of the big scientists to their universities that made them so vulnerable. In this country our crises are never so severe, for many reasons; yet it would be naive to assume that our scientists, and their students, have somehow retained intact the good old-fashioned virtues.

The political aspects of the most recent American student challenges indicate some conflicts of responsibility that naturally lead to considerations of loyalty. For there has arisen a conflict of responsibilities, roles and images, when university scientists, nominally "pure" and independent scholars, actually function as technicians on mission-oriented research. This contradictory situation leads to strains on the scientist's job. There is the delicacy of secret research (whose secrecy may also be a secret!) and there is a likelihood of the distortion of the criteria by which problems are chosen for research students. But most serious, there is an inducement to self-deception or hypocrisy, where the scientist sincerely claims the privileges and immunities appropriate to a member of a community of scholars (as in the indignant rejection of the idea that his university has anything to do with politics, while unself-consciously enjoying the power and material benefits accruing to him as a partner in industrial or military enterprise).

At this point we can truly speak of conflicts of loyalty, at least for those scientists who are not complete opportunists. To be sure, there is no simple opposition of loyalties here, between (say) national patriotism and the ideals of university scholarship. But never again, after the war-science scandals at American universities, will it be possible for scientists to assume that whatever is good for the Department (or Ministry) of Defence is good for their university. To the extent that a university scientist has loyalties with objects both within and without his institution, he will need to recognize genuine potential conflicts between them.

On the problem of conflicting loyalties of this sort, we are indebted to Professor Ernst Chain for providing us with the limiting cases, as it were, of possible solutions. His recent television performance dealt with a restricted case; those scientists who, in a democratic society, voluntarily become soldier-technicians. He believes that they thereby contract a lifelong obligation of obedience to their organization, otherwise they become "traitors". Apparently he would deny such scientists the rights and demands of conscience that an ordinary soldier has under the Nuremberg Code of war crimes. Sir Ernst's earlier essay was more bold and perhaps more consistent. There he asserted that the scientist's social responsibility entails a completely subservient loyalty to his employer and/or government. But there he did not mention political ideals as proper objects of loyalty, so we must conclude that a scientist under a Soviet or Nazi regime should obey his masters

similarly. Also, in the absence of any assurance to the contrary, we must assume that Professor Chain's scientist may not challenge the state in its definition of goals and problems of science. I find it difficult, therefore, to see grounds on which Lysenko would legitimately be opposed. And as a *reductio ad absurdum* of this position, one may question whether collecting specimens for Himmler's "anthropological" museum of *Untermenschen* was not a war crime but, by definition, a scientific exercise.

Of course such things could never happen here and so perhaps Professor Chain should not be required to follow his speculations to their possible logical conclusions. But even our democratic military technology can lead scientists to quite serious conflicts of loyalty. An example, discussed at the BSSRS teach-in at Durham last year, is the campaign of American computer experts against the proposed anti-ballistic missile system. They could see, and demonstrate, that such a system could not possibly operate to the standards of precision and reliability necessary for it, but the Pentagon did not want to know. So as a last resort, they took the law into their own hands and denounced the ABM system publicly. What loyalties impelled them to this extreme and potentially dangerous step? As "professionals" they could have derived great profit from a long and expensive series of fruitless attempts to improve this among other specious weapons systems. It must, therefore, have been loyalty to their own personal integrity to stop a particularly blatant bogus project and also to the human race, to prevent a "mistake".

I believe that, in such a case, there are genuine problems of conflict of loyalty in contemporary, industrialized science. Assuming the veracity of Goffman and Tamplin, they had just such a conflict when the Atomic Energy Commission told them to bring Sternglass's estimates of pre-natal deaths from fallout from several hundred thousand to absolute zero. It is possible that similar conflicts presented themselves to the scientists tasting the dangers of the insecticide dichlorvos in Vapona strips.

Such conflicts of loyalty involve very generalized and diffuse objects and principles and the scientific evidence on which they are based is frequently inconclusive. Hence they are inevitably controversial and—dare I say it—political. But it would be mistaken, and damaging, to regret their existence and to frame codes of practice under which they could not occur. For they represent the emergence of a new scientific conscience, and a new style of science, in response to the social conditions and social problems of industrialized science and science-based technology.

"Critical science" as practised by Linus Pauling, Rachel Carson, Barry Commoner, and the independent section of the environmental scientists, is the live and growing point of science today. Its members are doing for ourselves what the *Philosophes* of the Enlightenment did two centuries ago: exposing in detail and in principle the sterile and dehumanized common sense in which our present science and technology are conceived. To this movement, we are already indebted for the exposure of the institutionalized psychopathology of nuclear deterrence, the biochemical rape of Vietnam, the technomaniacs' obsession with bigger and faster means of transport, and the manifold pollution from "socially significant chemicals". At the fundamental level, it questions the identification of novelty with progress and makes us think again what science and technology are for.

Such work is fraught with difficulties and hazards. The ongoing work of society is done by specialists within institutions and so the critical scientist will always be needing to take food from the hand he is biting. Thus he will suffer correspondingly from conflicts of loyalty. But such scientists, who I believe are a small but rapidly growing minority among the units of the scientific-technical manpower pool, have a definite focus for their basic loyalties: to humanity, as stewards for nature. The conflicts they will inevitably experience can be creative, for themselves, for science and for us all.

Cretaceous Seafloor Spreading in the Western North Atlantic

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Magnetic profiles parallel to and between fracture zones in the Cretaceous western Atlantic suggest at least twenty-five reversals between 135 and 90 m.y. BP, with a long normal period between 80 and 90 m.y. BP. The fracture zones constrain the position of the America-Africa pole.

In 1968 a geomagnetic reversal time scale corresponding essentially to Tertiary and Quaternary time (77 to 0 m.y. BP) was proposed, based on magnetic anomalies imprinted on the oceanic basement by axial accretion at the Mid-Oceanic Ridge¹. For the period 5 to 0 m.y. BP, the reversal chronology has been calibrated against measurements of age and polarity made on rock specimens², and the portion of the reversal chronology¹ before 5 m.y. BP was later corroborated by the JOIDES deep sea drilling programme in the South Atlantic³ and the other oceans. The uncertainties in the absolute age of

reversals that occurred in the middle, or lower, part of the reversal chronology are probably no more than a few m.y., and the length of a particular normal or reversed period is probably known to an accuracy of about 0.1 m.y.⁴. Several slightly different reversal chronologies for post-10 m.y. BP time have been proposed⁵.

There are several reasons why extensions of the reversal chronology to Mesozoic or still older ocean floor that may be present have been slow in coming. Although about two-thirds of the ocean floor is Cainozoic, deep sea drilling dates suggest that the oldest oceanic crust dates from at least 180 m.y. BP. Therefore, 55% or more of the surviving magnetic reversal time scale is located in a third of the ocean. This oldest third is also rather deep, covered with more sediment, and more densely studded with seamounts, making it difficult to delineate the magnetic anomaly pattern and deduce a reversal chronology from it. Another factor is that the later Cretaceous seemed to have been a time of predominantly normal polarity⁶, producing little in the way of identifiable anomalies.

The first pre-Cainozoic reversal chronology was derived from a 300 km wide band of correlatable anomalies between 20° N and 45° N in the western Atlantic⁷. The correlatable anomaly train was named after the survey platform, USNS Keathley.

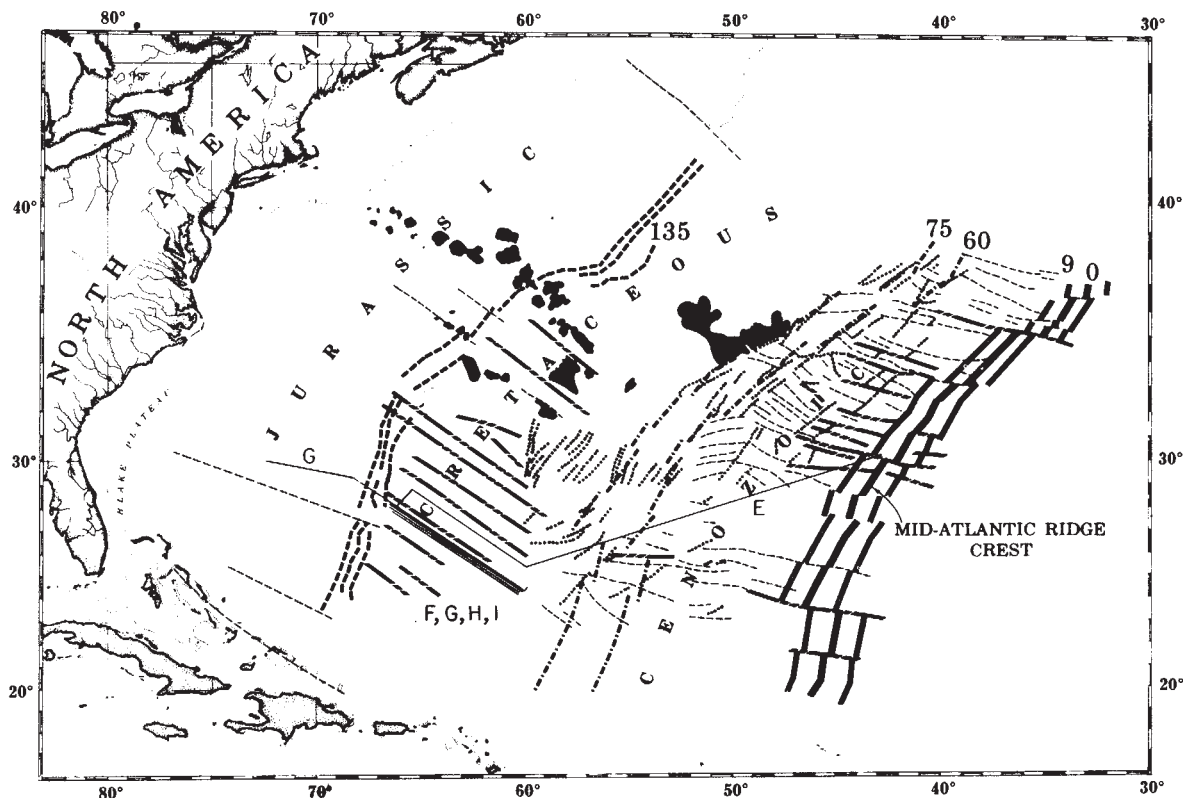


Fig. 1 Profile positions, superimposed on compilation of major isochrons, magnetic anomalies, and physiographic trends in the western North Atlantic¹⁷. Systematic surveying at 20 mile line spacing did not extend east of 60° W. Tracks are keyed to Figs. 2 and 3.

This "Keathley sequence" probably exists in the eastern Atlantic (although neither in the South Atlantic nor north of the Azores) and in the western Pacific⁷. From JOIDES drilling⁸ the Keathley sequence was generated between 155 and 135 m.y. BP, with the mean reversal rate⁷ close to the post-42 m.y. BP value¹ of 3 per million years.

The oldest Atlantic seafloor is represented by magnetic smooth zones about 500 km wide, lying between the Keathley sequence and the continental shelves west of North Africa and east of the United States. Extrapolation of JOIDES dates suggests the smooth zones were formed between 180 and 155 m.y. BP⁸. A preliminary study suggests that correlatable low amplitude (± 30 gammas) magnetic lineations exist in the magnetic smooth zone⁹. If these reflect geomagnetic reversals, the reversal rate for that period must have been of the same order as for the period 155 to 135 m.y. BP.

Cretaceous Reversal Anomaly Pattern

One of the least known parts of the post-180 m.y. BP geomagnetic reversal chronology is the time between the Keathley sequence⁷ (155 to 135 m.y. BP) and the Heirtzler time scale (77 to 0 m.y. BP)¹. In this article we offer several well oriented magnetic profiles to fill the whole of what is approximately Cretaceous time.

A detailed bathymetric-magnetic survey of the western North Atlantic^{7,10} revealed the Cretaceous crust east of the Keathley sequence to be densely fractured (Fig. 1). From the east-west tracks spaced 20 miles apart, and from other sounding data, fracture zones spaced about 100 km apart and trending N60W were identified (Fig. 2). Most of these fracture zones were apparently formed about 135 m.y. BP, a time of major spreading change in the North Atlantic, and probably the beginning of spreading in the South Atlantic⁷.

The paucity of fracture zones on the Keathley crust made it possible to correlate the anomalies, but by contrast, the east-west magnetic profiles across the post-Keathley seafloor showed uncorrelatable anomalies⁷. The numerous fracture zones (Figs. 1 and 2) help explain why no pattern emerged.

During the summer and autumn of 1970, however, it was possible, aboard USNS Lynch, to search for a Cretaceous reversal sequence, because the position and trend of fracture zones were by then known. Closely spaced and accurately navigated lines (Fig. 2) were run parallel to and between two prominent fracture zones in an area of relatively smooth basement. An additional line was placed one crustal block further north to determine whether possible anomalies correlate across a fracture zone (as they should, if they are due to reversals) and whether any such anomalies are offset across the fracture zone, presumed to be a transform fault.

The residual profiles are shown stacked from north to south in Fig. 3. A correlatable magnetic signature is strongly suggested, and we have confidently numbered the more prominent anomalies of this "Lynch sequence" as K-1, K-2 and so on, the K prefix standing for Cretaceous. This is in keeping with the anomaly prefix J for the Keathley sequence⁷, which is Jurassic in age⁸. We recommend the anomalies in the Heirtzler sequence¹ be assigned a prefix C for Cainozoic. The number scheme within both K and J sequences is in keeping with the precedent of Heirtzler *et al.*¹ in that numbers increase from youngest to oldest.

The K-anomaly correlations are tentatively shown in Fig. 3. Many more profiles will be required to identify all correlatable features. In particular, the oldest K-anomalies appear erratic, and we know the basement to be rough there. Thus, there is considerable doubt about the contribution made to the anomalies by magnetized basement relief. We intend to elaborate on this later (work to be published by P. R. Vogt and G. L. Johnson), when a model for the K-anomalies will be given. The middle K-anomalies are typical of reversal anomalies, and the basement under them is surprisingly smooth. At the young end, the relation to the Heirtzler anomaly sequence is still uncertain, as the fracture pattern east of 60° W is poorly known and the profile of Fig. 3 is oblique to the anomaly strike and probably cuts at least one fracture zone. The smooth zone between K-1 and K-2, however, apparently correlates with anomaly "R" identified just north of the Antilles⁷. This was evidently a long period of normal

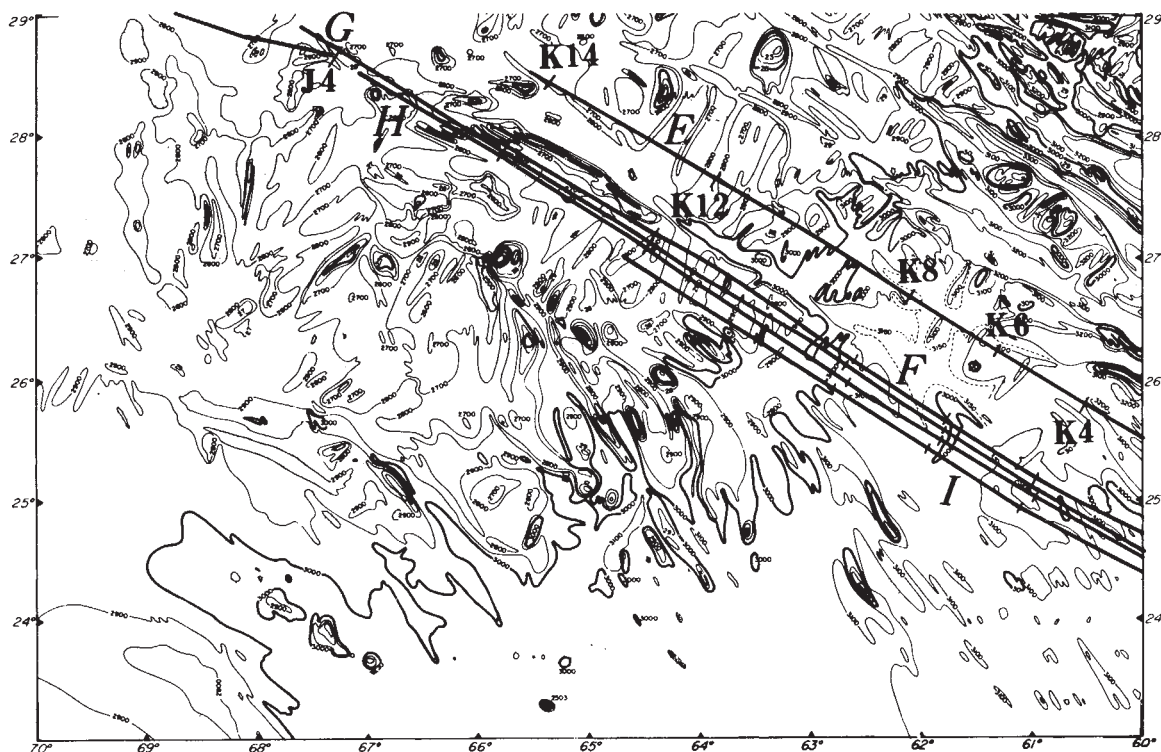


Fig. 2 Profile tracks collected by USNS Lynch, superposed on well charted lower Cretaceous seafloor on east flank of Bermuda Rise. Bathymetry from Johnson and Vogt¹⁰. Tracks and correlated anomalies are keyed to Fig. 3.

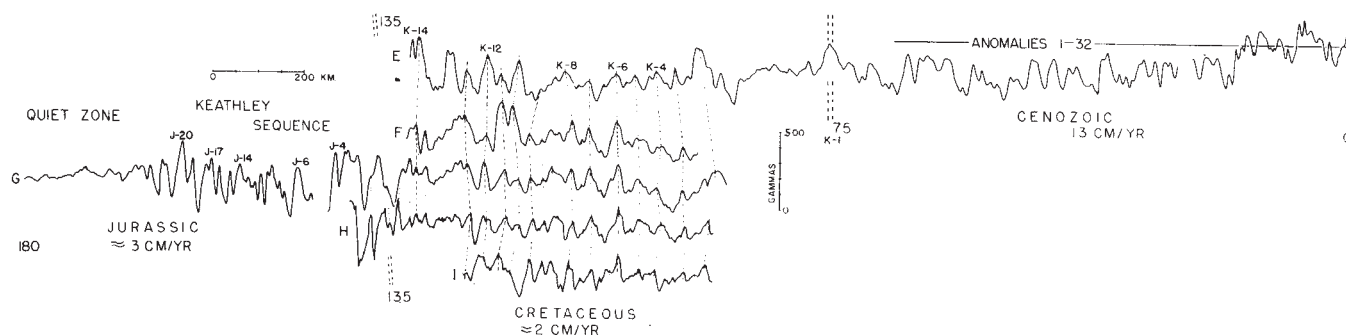


Fig. 3 Residual total field magnetic profiles. Suggested correlations that are more obvious are dashed and lesser features, possibly also correlatable, are dotted. Cretaceous (K) Lynch sequence is flanked by upper Jurassic Keathley sequence (J)⁷ and well known Cainozoic anomalies¹.

polarity in the Upper Cretaceous⁶. If our identification is correct, K-1 and the smooth zone west of it (Fig. 3) may be identical to anomaly 33, a long period of normal polarity reportedly found in the Atlantic and Pacific basins¹¹. Based on JOIDES drilling and extrapolations from Cainozoic anomalies, the long normal period lasted from about 90 to 80 m.y. BP.

The existence of numerous correlatable anomalies in the Cretaceous North Atlantic seems to conflict with the rather uniform Cretaceous smooth zone, indicating few or no reversals, reportedly found in the South Atlantic¹². We agree that polarity was constant between magnetic highs K-1 and K-2, and possibly also between K-13 and K-14 (Fig. 3). These periods however, represent only a fraction of the Cretaceous. Unless South Atlantic lineations were subsequently erased (or our lineations are not the result of reversals), we have no explanations for this disagreement. If the Cretaceous were largely free of reversals, anomalies might still be created by variations in dipole intensity, but the anomalies should then be found in the South Atlantic also. Furthermore, a South Atlantic magnetic smooth zone of Cretaceous age cannot be due to spreading at equatorial latitudes. Another unlikely alternative is that variations in layer thickness or axial demagnetization produced the K-anomalies shown in Fig. 3. A more reasonable explanation, perhaps, is that anomalies K-2 through K-14 never gained respectable amplitudes in the South Atlantic because the early rift axis was kept inundated by sediment. Such conditions should inhibit the formation of a rapidly cooled, highly magnetized pillow lava layer. This explanation was invoked as a possibility for the older North Atlantic smooth zones¹³.

In summary we feel confident that the K-anomalies shown in Fig. 3 represent geomagnetic reversals occurring during Cretaceous time. Neglecting the long normal period between about 90 and 80 m.y. BP, we conclude that at least twenty-six reversals, represented by 13 positive anomalies, occurred between 135 and 90 m.y. BP. This suggests a reversal rate of greater than 0.6 per million years. If the minor anomalous features, shown dotted in Fig. 3, are also interpreted as due to reversals, the reversal rate for the period 135 to 90 m.y. BP would have been close to 1 per million years, that is, about the same as for the period 77 to 42 m.y. BP¹. It seems certain, however, that the 135 to 90 m.y. BP reversal rate was lower than the 155 to 135 m.y. BP and 42 to 0 m.y. BP values.

The results above conflict somewhat with land-based palaeomagnetic measurements from the Cretaceous, described by Helsley and Steiner⁶. The rock sample data show the Cretaceous to be predominantly normal, with the exception of two reversed intervals in the Maestrichtian (70–60 m.y. BP), one in the Santonian (78 m.y. BP), one at the Albian–Aptian boundary (110 m.y. BP) and two in the Neocomian (130–140 m.y. BP). The absence of known reversals between 109 and 77 m.y. BP and between 129 and 102 m.y. BP (all ages being interpolated from the data of Helsley and Steiner⁶) contradicts

the anomaly data of Fig. 3. Possibly the zone between anomalies K-13 and K-14 corresponds to the later part of the 129 to 102 m.y. BP normal intervals, but there is still a serious overabundance of measured normal polarities, compared with the anomaly data. There are two ways to resolve this: (1) palaeomagnetic sampling in the Cretaceous has been severely non-random, skewed toward normal intervals; or (2) the observed anomalies are due in large measure to basement structures or geomagnetic intensity fluctuations. We prefer the first explanation.

America–Africa Plate Rotation Pole during Cretaceous

The bathymetry of what JOIDES drilling suggests to be seafloor of Lower and Middle Cretaceous time (Fig. 2) is now

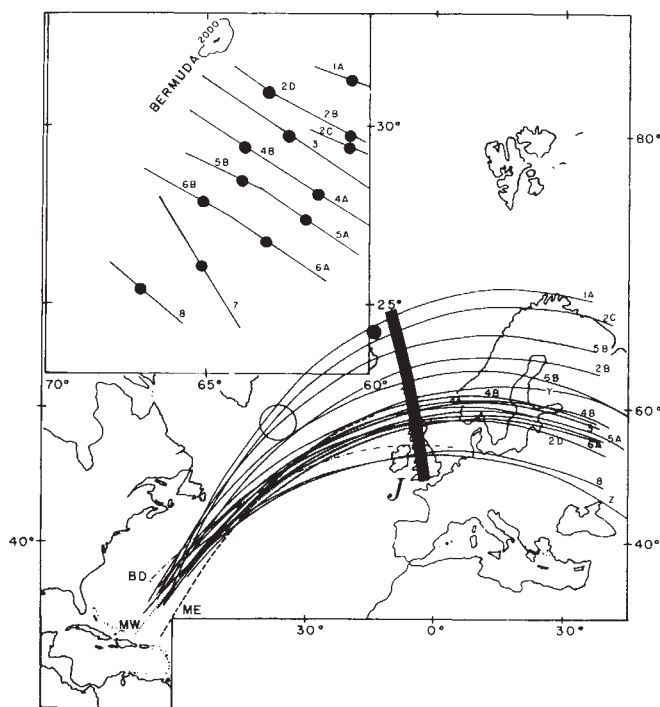


Fig. 4 Great circles normal to Cretaceous fracture zones (Figs. 1 and 2) clearly miss the late Tertiary America–Africa pole¹⁶, shown as open circle, and the net or total opening pole, shown as filled circle¹⁵. BD is a fracture zone extending into the younger Keathley crust near Bermuda. MW and ME are magnetic anomalies probably associated with fracture zones about 100 km north of the Puerto Rico Trench¹⁴. Preferred pole is in shaded region, but even this is far from certain. Arc labelled J applies to Jurassic Keathley sequence; its intersection with great circles would give the virtual pole if the pole position did not change from Jurassic to Cretaceous.

charted with sufficient accuracy to disclose the positions and trends of major fracture zones¹⁰. In all likelihood, the fracture zones are transform faults, and therefore form portions of small circles described about the virtual plate rotation pole for the Cretaceous western Atlantic. To locate this pole, we constructed great circles normal to most of the fracture zones, in some cases at several points along a single fault (Fig. 4). We also interpret the linear south-east trending magnetic anomalies north of Puerto Rico¹⁴ as lying along fracture zones. The great circles lie along a well defined band, but the position of the pole, somewhere along the band, is uncertain. The rate of northward narrowing of the K-anomalies (Fig. 1) will resolve this problem when it becomes known. In any case, it is clear from Fig. 4 that the pole coincides neither with the net Africa-America pole¹⁵ nor with the later Tertiary pole¹⁶.

In conclusion, five carefully oriented magnetic profiles suggest at least twenty-six geomagnetic reversals recorded as magnetic reversals on the lower and middle Cretaceous (135 to 90 m.y. BP) seafloor of the western North Atlantic. With less certainty, a long normal period occurred between 90 and 80 m.y. BP. Fracture zones give a good great circle azimuth to the 135–90 m.y. BP America–Africa virtual plate rotation pole, but the pole position along that azimuth remains uncertain.

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General Model for the Chromosomes of Higher Organisms

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The model suggests that chromosomal DNA falls into two classes: globular DNA (containing unpaired regions for control) and a much smaller fraction consisting of fibrous DNA which alone codes for proteins.

I WISH to propose a general model for the structure of the chromosomes of higher organisms*. This model is derived from ideas and data from many sources†. Because I have found it impossible to set out my ideas and the supporting evidence in a short space, I merely summarize here my conclusions. A much fuller account is in preparation and will be submitted for publication in the near future.

The model assumes that the DNA in a chromatid is a very long mononeme (see the review by Prescott² and the recent careful work by Laird³), which probably runs continuously from one end of the chromatid to the other.

* I have used the term higher organisms rather than eukaryotes because I want to avoid having to discuss, at this stage, the chromosomes of various lower eukaryotes such as the dinoflagellates and the fungi.

† Proper acknowledgments will be given in the fuller paper, but I cannot refrain from mentioning here the very stimulating theoretical paper by R. J. Britten and E. H. Davidson¹, which the reader is strongly recommended to read in parallel with this one. It contains extensive references to the earlier literature.

The model has three basic features. (1) The coding sequences of the DNA (that is, all those sequences which code for polypeptide chains) are postulated to be mainly, if not entirely, in the interbands (as visualized in the giant polytene chromosomes of the Diptera⁴). The bands, which contain all but a few per cent of the DNA, are identified as the control elements. This is illustrated diagrammatically in Fig. 1. A genetic complementation group is usually contained in a band plus an interband.

Thus on this view most of the DNA in higher organisms does not code for proteins but is used for control purposes, as already suggested by F. Vogel⁶ in 1964. I have calculated that the average‡ amount of DNA (per mononeme) in an interband of *Drosophila*^{7,8} is enough to code for an "average" protein of molecular weight 30,000–40,000. I have, therefore, adopted this speculation as a good working hypothesis.

(2) The central idea is that the recognition sites, needed for control purposes in higher organisms, are mainly unpaired single stranded stretches of double stranded DNA. I call this the Unpairing Postulate and it is set out diagrammatically in Fig. 2. It has been derived from a theoretical consideration of the general nature of protein molecules and the probable variety and length of the base sequences which need to be recognized in higher organisms. A particular type of example of this postulate has already been put forward by Gierer⁹.

The argument I give is a general one. It springs from the

‡ The average amount of DNA in the mononeme of an interband had been estimated previously by Beermann⁴.

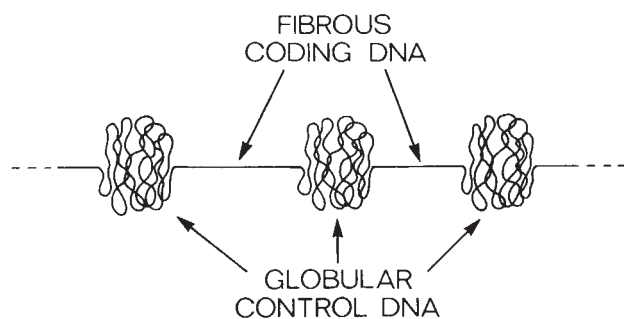


Fig. 1 An extremely schematic drawing of the proposed general structure of the DNA of the chromatid. The line represents part of the continuous DNA molecule in the mononemic chromatid. The straight portions correspond to the interband regions of the giant polytene chromosomes of the Diptera, which are postulated to be similar in their general character to the corresponding interphase chromatids, which are the active form. The mitotic chromosome is relatively inert⁵. The DNA sequences coding for protein are postulated to be mainly, if not entirely, in these extended regions. For convenience this DNA is referred to as fibrous DNA. The intricately folded regions correspond to the bands seen in the polytene chromosome^{4,7}. No attempt has been made to represent their detailed structure. They are postulated to be the sites of the control regions. The model implies that a genetic complementation group is usually contained in either an interband plus a band or an interband plus part of the bands on either side. When a gene is active the bands are probably at least partly unfolded⁴. The globular DNA is certainly complexed with chromosomal proteins¹⁰, the fibrous DNA probably so. Thus both should be more strictly referred to as nucleoprotein.

fact that for all proteins whose tertiary structure is known, the active site is, to a first approximation, a shallow groove or a cavity and not a protruding piece of the protein structure. The former structures can rather easily be made to provide highly specific interactions, both with small molecules or with extended polymers. However, in double-helical nucleic acid the specific groups on the bases are not protruding but are themselves in one or other of the two grooves formed by the phosphate-sugar backbones. Thus, it might not be easy to design a protein of reasonable size to recognize more than a limited number of base pairs, especially when one remembers the twisted nature of the normal double helix. The postulate has even more force if single stranded RNA is also used to recognize the control sequences on the DNA, as favoured (with reservations) by Britten and Davidson¹.

My argument is that when very large numbers of different sequences need to be recognized (which implies that the sequences must not be too short), it will pay to unwind the double helix before recognition. This may be expensive to arrange but in the long run it will provide a much greater abundance of versatility.

(3) The forces and energy needed to unpair the recognition stretches of the DNA are provided by the combination of the DNA with chromosomal proteins—probably the histones¹⁰. Although the three-dimensional configuration of a band may be very intricate, such globular structures may be based on structural motifs of various kinds. The most obvious one is a simple supercoiled DNA, that is, a helical double helix, as already suggested by various workers^{11,12}, but other more complicated structures are possible¹¹. One such example is illustrated in Fig. 3. As far as I know this suggestion is a novel one.

The general property of this family of structures is that there are lengths (probably of hundreds of base pairs) of DNA whose exact base sequence matters very little, interspersed with shorter stretches (perhaps of a hundred bases or so) of specific sequences which are probably repeated at very many places along the DNA. On this view the role of the histones is not merely to cover up the DNA but to help the DNA to expose itself in the right places.

Plausible general reasons can be given why the bands (the

control elements) are so large compared with the interbands (the coding elements). In the first place, the type of structural motif outlined in Fig. 3 cannot be constructed on too small a scale. Moreover, as Britten and Davidson¹ have pointed out in their Fig. 14, multiple control elements may well be needed adjacent to each particular coding sequence. In addition, a set of similar elements may be required within certain bands to help provide a graded response. Finally, it appears to be a general rule that intricate three-dimensional biological structures are always bigger than one might naively expect. The examples of globular proteins, transfer RNA and ribosomes spring to mind.

My fuller paper will discuss possible mechanisms for the formation during evolution of these large control regions. It would seem likely that both tandem repetition and translocation will be involved. Whatever the origin of tandemly replicated sequences (satellite DNA¹³ or otherwise), when they are first formed there will be an exact repeat of the sequences both in the paired region (such as the stem of Fig. 3) and in the regions which become unpaired (such as the loop of Fig. 3). However, during evolution, mutations will accumulate at different rates in these different regions. The paired regions will diverge rapidly, since the exact base sequences there do not matter appreciably, but changes in the unpaired regions will occur less rapidly, if at all, because they have to interact with other molecules during control operations. Thus, newly evolved bands (or parts of bands) would be expected to have a closer degree of tandem repetition of their base sequences than phylogenetically older ones.

The model, in its simplest form, suggests that the number of different proteins normally produced by higher organisms may not be much more than a few thousand for *Drosophila* and

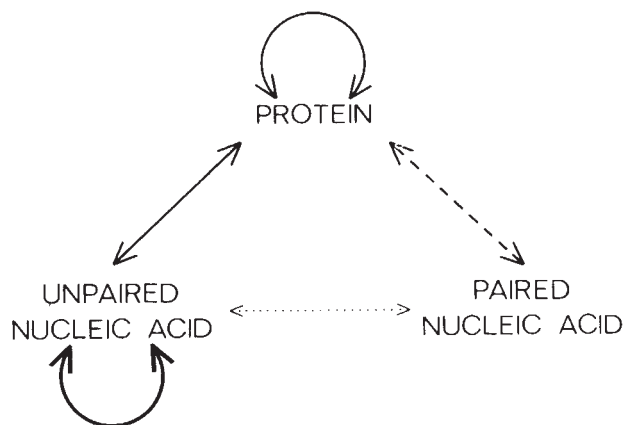
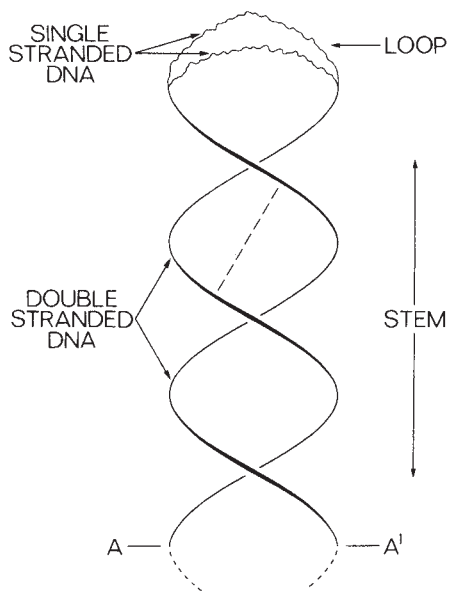


Fig. 2 Each line represents the possibility of a highly specific interaction between two macromolecules. One molecule is from the class at one end of the double arrow and the other is from the class at the other end. Notice that no distinction is made between RNA and DNA. Instead, a strong distinction is made between paired nucleic acid (meaning a stretch of double helix) and unpaired nucleic acid which can be either single stranded nucleic acid or unwound stretches of an originally double helical structure. The latter may or may not be refolded to some extent into three-dimensional structures having a complex mixture of paired and unpaired regions⁹ such as is found in transfer RNA. The dotted line represents the formation of a triple helix, such as poly A + 2 poly U. The dashed line represents the recognition by a specific protein molecule of a particular base sequence of base-paired double stranded nucleic acid. The solid lines represent interactions of abundant versatility. The very thick line emphasizes that for any sequence of the usual monomers (base sequence) there is always a complementary base sequence. The diagram does not deal with relatively unspecific interactions, such as the interaction between a particular protein and a DNA backbone independent of the latter's base sequence. The Unpairing Postulate states that the interactions used for control in higher organisms will mainly be chosen from those shown by solid lines in the figure. This implies that double helical DNA will usually have to be unwound at the recognition sites.



some tens of thousands for man. It is not, however, completely excluded that, in special cases, multiple coding sequences may be hidden within some of the globular bands, in which case the numbers could be higher. The amount of these special bands, if they exist, might differ markedly in different kinds of higher organisms.

The model, which is logically coherent, appears to me to be compatible with a very large amount of experimental data obtained using very different techniques. These include rough estimates from genetic data¹⁶ of the number of "genes" in *Drosophila* and man, the correlation between the number of bands plus-interbands and genetic complementation groups¹⁷, the specific pairing between the bands of the giant polytene chromosomes⁷ shown by the study of inversions and so on, the nature¹³⁻¹⁵ and general effects of the heterochromatin¹⁸, the large amount of data on nucleic acid hybridization^{1,19} and the formation of circles by the technique of Thomas and his colleagues²⁰.

It can also be accommodated to the data on the "puffing" of polytene chromosomes⁴, the general nature of the heterogeneous rapidly turning over nuclear RNA²¹⁻²⁴ and the apparent absence of polycistronic messengers in higher organisms. It is not incompatible with the very scanty X-ray studies of chromatin^{12,25} and the electron microscope pictures and measurements¹¹.

Although the model is speculative and not fully detailed, and raises at least as many questions as it attempts to answer, I hope it may serve as a focus for discussion and for the design of experiments.

In addition to thanking many colleagues for their patience in explaining their results and for discussing these problems with me, especially Sydney Brenner, Leslie Orgel, Peter Walker (see his remarks reported in ref. 26), Gordy Tomkins and David Baillie, I thank especially the organizers of the specialists' meeting in May of this year at Port Cros²⁶ for inviting me to attend.

Note added in proof. On the amount of informational DNA in higher organisms see T. Ohta and M. Kimura, *Nature*, **233**, 118 (1971).

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LETTERS TO NATURE

PHYSICAL SCIENCES

Charged Particle Track Registration in Amber

IONIZING charged particles can leave damage trails in certain dielectric solids which, in suitable conditions, can be chemically etched into visible, usually cone-shaped, tracks¹⁻³. Such tracks have been widely studied in minerals, glasses, and synthetic polymers⁴, but damage tracks in natural resin solids such as amber have not previously been studied.

Some amber deposits in England⁵ are of Carboniferous age (345 to 280 m.y.) whereas the age of Baltic deposits^{5,6} is thought to be Eocene-Oligocene (about 40 m.y.). Amber samples may, therefore, have recorded certain rare cosmic ray events such as the passage of magnetic monopoles. Furthermore, if ²³⁸U spontaneous fission fragment trails are preserved in the amber for a sufficiently long time, then in principle the track dating technique^{4,7-9} should be applicable to the dating of amber deposits. In this communication we describe the etching of fission fragment tracks in amber and present data on the ionization damage threshold for track registration, on the annealing of formed tracks, and on the abundance of ²³⁸U.

A quite satisfactory etching solution for amber was found to be 30 g of K₂Cr₂O₇ in 150 cm³ of H₂SO₄ (33%). Fission fragment tracks from ²⁵²Cf could be observed after etching for 1 h at a temperature of 75° C. At lower temperatures, the etching rate was much lower but the ratio of etching rate, V_T , along the particle track to general surface etching rate, V_g , increased and the half-cone angle at the tip of the track, given by $\arcsin(V_g/V_T)$ decreased, a most desirable trend because both particle track visibility and the maximum incidence angle relative to the material surface for track registration are thus improved. At 28° C, the cone angle was found to be $38^\circ \pm 5^\circ$, at 40° C it was $42^\circ \pm 5^\circ$, at 78° C it was $60^\circ \pm 8^\circ$, and at 90° C no tracks were observed. Typical ²⁵²Cf fission fragment tracks after etching at 40° C are shown in Fig. 1. This etching temperature was used throughout the work to be described.

All synthetic plastics studied so far have significantly lower ionization damage thresholds for particle track registration than crystalline solids, minerals, or glasses¹⁰. The very complicated differential etching process as well as the complex details of damage formation have precluded the formulation of a quantitative theory of track registration. Qualitatively, it has been thought that the ionization damage leading to track formation in plastics is lower because polymer chains are more readily broken in a plastic than atomic displacements are produced in a crystal or glass. These qualitative features are represented in the so-called "ion-spike" model of track formation¹⁰. Amber, being a resin material, would be expected to have a lower threshold than minerals or glasses but we find that it has a very high threshold, larger even than those of the meteoritic minerals which have the highest of the previously measured thresholds.

Table 1 shows the track formation properties of amber relative to mica (muscovite) as studied using slowed ²⁵²Cf fission fragments. Various thicknesses of polycarbonate

Table 1 Track Formation of Amber relative to Mica and Diopside

Absorber thickness (mg cm ⁻²)	Track density relative to that of mica at zero absorber thickness			
	Mica	Amber	Diopside ^{3,11}	Mica ^{3,11}
0.88	1	1		
1.1	1	1/2		
1.32	1	1/10		
1.476			> 1/2	
1.54		0		
1.607			0	> 1/2
1.76	1/2			
1.914				0
1.98	1/10			
2.2	0			

sheets were placed between the fission source and the amber and mica samples, which were then irradiated for identical times. The agreement between the earlier results for mica and diopside^{3,11} and the results of our work is satisfactory in view of the 10% uncertainty in absorber thickness. There were no tracks formed by ion beams of ²⁰Ne at 10 MeV a.m.u.⁻¹ and ³⁷Cl at 2 MeV a.m.u.⁻¹ at normal incidence.

Track fading can occur due to thermal annealing of the damage regions^{4,7-9}. Phenomenologically, the fading can be

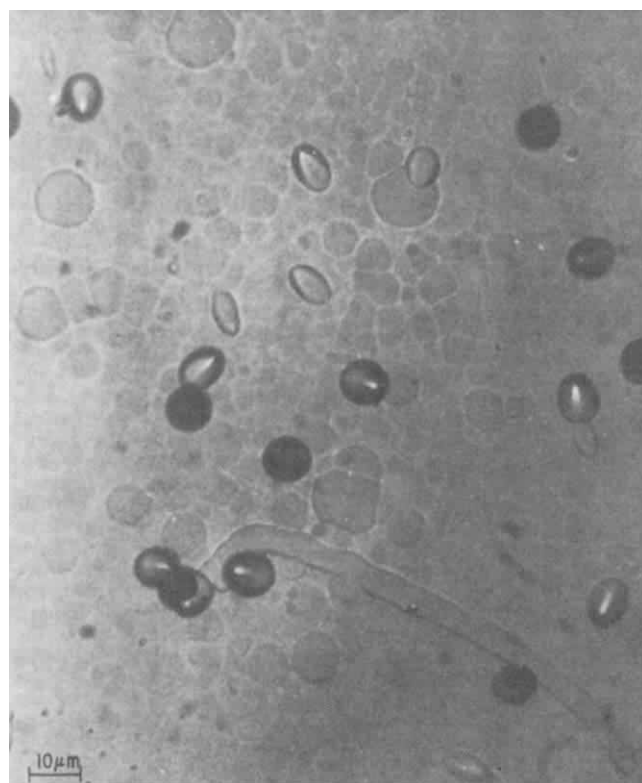


Fig. 1 ²⁵²Cf fission fragment tracks in amber.

described in the form

$$\tau = A \exp(E/kT) \quad (1)$$

where τ is time required for a certain degree of track fading. The activation energy E and the factor A can be determined by several measurements of track fading at different temperatures. It is then assumed that this relationship can be extrapolated to geological times. In those instances where verification was possible, this extrapolation has proved to be valid⁴

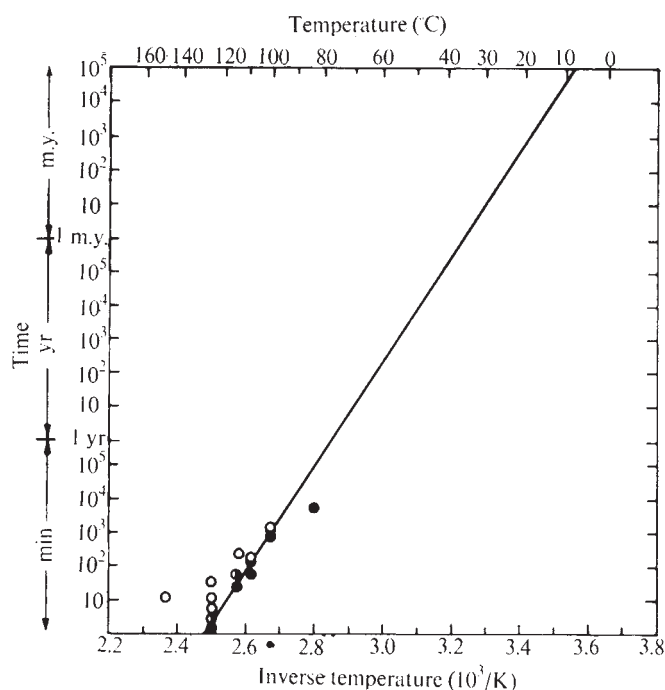


Fig. 2 Fission fragment track fading results for amber. —, Approximate onset of fading; ●, tracks not faded; ◐, partial track fading; ○, total track fading.

Annealing effects for amber in accordance with equation (1) are shown in Fig. 2; ²⁵²Cf fission fragments were again used. An activation energy of 3 eV can be deduced from the slope of the data on complete removal of tracks. An exposure of 1 h at 115° C was sufficient to remove fission fragment tracks completely. We conclude that, at a mean temperature of 30° C, fission tracks from ²³⁸U decay are retained for approximately 10 m.y., and at 20° C for 450 m.y. Given a sufficient uranium abundance, it would seem that amber would be suited to the particle track technique of dating^{4,7-9}. The deposition of amber in relatively shallow strata or marine basins would not heat the material above 30° C for long periods. Therefore, from Fig. 2, we may conclude that the tracks from ²³⁸U fission would remain from the fossilization period to the present time. Because age determination from stratigraphic and palaeontological data is relatively poor and because no other radiometric dating on amber has been successful⁵, the track technique may potentially provide unique information on amber age.

It is unfortunate that the great age of amber is not coupled with a lower track registration threshold. Mica (muscovite) and obsidian have been scanned for magnetic monopole tracks and these studies have set rather stringent limits on the flux of magnetic monopoles of various masses and magnetic charge numbers greater than 2 (ref. 12). The high threshold of amber precludes its use for registering monopoles of charge 1 and charge 2, and allows it to be used only in a monopole charge-mass region which has already been well explored¹³.

Uranium abundance in amber has not been reported previously. We have determined the ²³⁸U content in our amber

samples (collected near Gdansk, Poland) by inducing ²³⁵U fission and then observing the fragment tracks¹⁴. Because of heating effects in reactor neutron irradiations we chose to count the induced ²³⁵U fission events not in the amber but in mica placed immediately around the amber sample*. The same neutron dose irradiated the mica-amber-mica sandwiches as well as two mica-glass-mica dosimetry samples. From the known U content of the glass we have deduced the ²³⁸U abundance in seven different amber pieces. The average ²³⁸U content of samples 1, 2, 3, and 5 is approximately 0.001 to 0.004 p.p.m. by weight. Samples 4 and 6 contain 0.5 to 0.7 p.p.m. and sample 7 has 0.03 to 0.08 p.p.m. In sample 4, large quantities of impurities were present as visible inclusions dispersed throughout the amber. On the other hand, sample 6 was free of particles but contained densely dispersed bubbles. These last two samples could not be scanned very effectively because of the surface imperfections due to inclusions and bubbles.

No natural fission tracks were observed for an effective scan area of 0.3 cm² on samples 4 and 6. Thus the oldest track storage age consistent with both the annealing curve and the measured ²³⁸U abundance is about 350,000 yr for a 90% confidence level (for Poisson statistics there is a 10% probability for zero events if the mean number of events is 2.3). If the samples are older, as indeed it is believed that they might be, then they evidently remained at temperatures above 35° C for most of the time. A very careful scan of sample 2 over an area of 3 cm² revealed no tracks. We estimate the maximum retention age, with a uranium content of two parts per billion, to be 8 m.y. (90% confidence level).

Although we were careful not to expose the amber specimens to track annealing temperatures, we have no knowledge of the thermal history of our amber samples. If we assume that no track annealing has occurred recently, there are several other possible explanations for the absence of natural fission tracks. The amber samples may be much younger than the country rock in the Baltic region and the mean temperatures of samples 4, 6, and 2 may have been about 37° C, 37° C, and 30° C respectively. It is also possible that the extrapolation of the annealing curve to geological times is not valid for amber.

Although amber is not suitable for observing magnetic monopoles of charge 1, the high threshold of amber indicates that it may well be a useful solid track detector in studies that require rejection of events caused by lightly ionizing fission fragments or similar particles. Whether the absence of natural fission tracks in amber is peculiar to our samples or whether it is a result to be generally expected for amber is a question that needs further examination.

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Time Dependence of Variances of Sonic Boom Waveform

In a series of experiments¹ performed in November and December 1966, at Edwards Air Force Base, California, sonic boom pressure signatures were recorded at forty-two ground level microphones, equally spaced in an 8,000 foot linear array, during level overflights of F-104 fighter aircraft at flight Mach numbers of approximately 1.3 and at an altitude of approximately 30,000 feet. The array was almost directly beneath the flight track. The variations in the signatures recorded by different microphones during the same overflight are believed to be caused primarily by atmospheric turbulence. This communication reports an analysis of the variations in these data and considers the extent to which the analysis substantiates a recent theory².

Crow's theoretical model consists of a linearized first order transient scattering theory for an initially plane wave step of overpressure incident on the Earth's turbulent boundary layer from above. The turbulence is considered isotropic and quasi-homogeneous. Eddies in the Kolmogorov inertial subrange (where turbulent structure functions vary with separation distance r as $r^{2/3}$) are considered to be the chief source of the waveform variations for times somewhat later than the principal shock arrival. An important result of the analysis is the relation

$$\langle \psi^2(t) \rangle = (t/t_c)^{-7/6} \quad (1)$$

for the ensemble average of the square of the ratio $(p^s)/\Delta p_0$. Here (p^s) is the scattered wave minus a phase shift term (formally appearing as a multiple of a Dirac delta function), which represents the increment that may be added to the incident wave to account (to first order) for the change in time of onset caused by transit speed fluctuations. The quantity Δp_0 is the overpressure of the incident step pulse. The parameter t_c is a somewhat complicated function of (height dependent) parameters characterizing the atmosphere's state of turbulence in the inertial subrange.

Although a previous experimental check on Crow's theoretical relation has been made by Bauer and Bagley³, using waveforms recorded on the wall of an extended ballistic range, with boundary layer turbulence created by a jet adjacent to the wall, the results are somewhat ambiguous because of the dissimilarity between the laboratory turbulence and that of the atmosphere. Our analysis is, however, based on actual field data.

We consider the set of forty-two microphone pressure signatures recorded during a given overflight to constitute a representative sample of what might be obtained during an ensemble of similar experiments. The choice of time origin for any given sample is taken as that time at which the overpressure first reaches 1/3 its peak value (see inset in Fig. 1). This choice is based on the premise that Crow's equation (1) is intended to apply when t is relative to time of actual wave onset. Onset is difficult to define unambiguously for waveforms with finite rise times, so some specific definition of onset must be made. It would appear, however, that any results comparable to those reported here are relatively insensitive to this definition.

The mean waveform $\langle p \rangle$ and variance $\langle \{p - \langle p \rangle\}^2 \rangle$ are estimated from a computation of the numerical averages

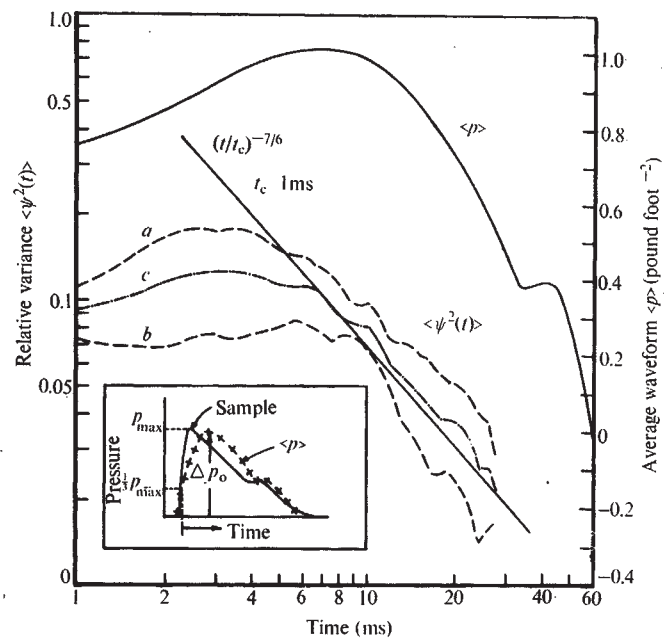


Fig. 1 Time variation of relative variance $\langle \psi^2(t) \rangle$ and of mean overpressure $\langle p \rangle$ of sonic boom waveforms. The three plots of $\langle \psi^2(t) \rangle$ correspond to computations based on data corresponding to (a) flight 16, (b) flight 17 and (c) combined data for both flights. The single graph of $\langle p \rangle$ corresponds to the combined set of data. The inset indicates the choice of time origin for sample waveforms, as well as the definition of maximum overpressure Δp_0 of the mean waveform. The negative phase of the waveform is not sketched.

of $p_i(t)$ and $\{p_i(t) - p_{\text{ave}}(t)\}^2$ for the set of sample signatures. The relative variance $\langle \psi^2(t) \rangle$ is defined as

$$\langle \psi^2(t) \rangle = \langle \{p - \langle p \rangle\}^2 \rangle / (\Delta p_0)^2 \quad (2)$$

where Δp_0 is the peak overpressure of the average waveform, is estimated similarly. Although sonic boom signatures are shaped somewhat like the letter N, a correspondence between this quantity and the $\langle \psi^2(t) \rangle$ in Crow's theory is expected to hold for times at which the variations are approximately equivalent to those induced by the propagation of a step pulse.

In Fig. 1, the derived estimates of $\langle p \rangle$ and $\langle \psi^2(t) \rangle$ are plotted for the set of sample signatures corresponding to flight 16, flight 17 and flights 16 and 17 combined. These flights were at 2145 GMT on November 20, 1966, and were spaced approximately 0.5 min apart. As it seemed doubtful whether the parameters characterizing the statistics of the atmosphere's state of turbulence would change appreciably during such a short time, the third computation treated the two sets of data as belonging to the same ensemble. Because any estimate of a variance from a limited number of samples is expected to improve with the number of samples (the expected error decreases as $1/\sqrt{N}$ or a Gaussian distribution) the estimate based on the combined data is considered to be the more accurate. The discrepancy between the three plots should give an indication of the possible range of error in our estimates. (The plot of $\langle \psi^2(t) \rangle$ against time is full log.) Thus during any range of time for which Crow's theoretical relation, equation (1), holds, the plot should approximate a straight line with slope $-7/6$. This seems to be very nearly the case for all three variance curves for times between about 7 and 27 ms. The start of this $-7/6$ regime appears to coincide with the time at which the average waveforms attain their maximum. The upper time limit would seem to correspond roughly to the time at which the second shock begins to arrive. The estimated corresponding value of t_c from the combined data for this particular time, place, and flight profile is very nearly 1 ms with an estimated error of ± 0.2 ms.

We believe that these results provide substantial support for Crow's theory, provided that the range of t in equation (1) is suitably restricted. The fact that the theory would appear inadequate to account for the variations in the first few ms is not surprising because of the nature of the approximations made in the course of Crow's derivation.

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Experimental Demonstration that the Couple on a Bar Magnet depends on H , not B

In the macroscopic theory of electromagnetism there are several systems of equations that are compatible with SI units^{1,2}. Among these are two important ones in current use which differ in their treatment of certain magnetic quantities. In one of these, introduced by Giorgi³, but now named after Kennelly, the field acting on a magnetic pole is considered to be the H -field, giving the couple T acting on a long thin magnet of moment j immersed in a linear magnetic medium as

$$T = j \times H \quad (\text{Kennelly}) \quad (1)$$

The degree of magnetization of a material is denoted in this system by

$$J = B - \mu_0 H \quad (\text{Kennelly}) \quad (2)$$

In the other system, introduced by Sommerfeld^{4,5} (but differing from the one attributed to him by the Coulomb's Law Committee¹⁸), emphasis is placed on the B -field and the equation for the couple on a long thin magnet of moment m is

$$T = m \times B \quad (\text{Sommerfeld}) \quad (3)$$

In this system the degree of magnetization of a material is represented by the quantity

$$M = B/\mu_0 - H \quad (\text{Sommerfeld}) \quad (4)$$

There is no difference between the Kennelly and Sommerfeld systems as far as the measures of B and H are concerned.

The relative merits of these systems of equations are a matter of current controversy and the use, without explicit specification, of alternatives within the commonly adopted framework of SI units is a source of much confusion. The International Electrotechnical Commission^{6,7} recognizes both systems and specifies names, symbols and definitions for all four quantities j , J , m and M ; the definitions of j and m are based on equations (1) and (3) respectively. The International Union of Pure and Applied Physics^{8,9} and the Royal Society¹⁰ have, however, omitted the Kennelly moment (j) from their lists of recommended symbols although they retain the magnetic polarization J . The Institution of Electrical Engineers gives no symbol for any of these quantities in its list¹¹, but it quotes the Bohr magneton in Kennelly units. SI itself is a system of units¹² and, although it specifies the appropriate unit for each physical quantity once that quantity is defined, it makes no statement about the merits of different systems of equations¹³. It is systems of equations that are being considered in this communication.

The choice between the Kennelly and Sommerfeld systems of equations is often said to be quite arbitrary (ref. 14, for example). This is not the case, as can be seen from the

following argument. In any reasonable system one expects that "the whole is the sum of its parts" and, in this context, this implies that the moment of a magnet should be given by the integral of its magnetic polarization (or magnetization) over the volume of the magnet itself. This is expressed by the equations

$$j = JdV \quad (\text{Kennelly}) \quad (5)$$

$$m = JMdV \quad (\text{Sommerfeld}) \quad (6)$$

Comparison of equations (2) and (4) shows that J and M at any point in a material differ only by the force constant μ_0 and equations (5) and (6) therefore imply that for any magnet

$$j = \mu_0 m \quad (7)$$

Now a long thin magnet immersed in a linear permeable fluid medium and subjected to an external magnetic field $B = \mu_r \mu_0 H$ experiences an observable couple given by equations (1) and (3). Comparison of these equations shows that

$$j = \mu_r \mu_0 m \quad (8)$$

which is contrary to equation (7). The equations of the set (1) to (6) are therefore not mutually compatible. The error may be located in various places depending on one's point of view. If we take equations (2), (4), (5) and (6) as definitions of J , M , j and m , then equations (1) and (3) predict different values for the couple on a long thin magnet immersed in a permeable medium. One of these two equations must therefore be wrong. If, however, equations (1) and (3) are treated as definitions of j and m , we find that, even for a "hard" magnet, j and m cannot both be independent of the surrounding medium and equations (2), (4), (5) and (6) cannot all be true.

This problem is important, not because magnets immersed in media are of practical significance, but because it impinges on fundamental questions about the formulation of the macroscopic theory of electromagnetism. The topic was first raised many years ago. Maxwell followed what is essentially the Kennelly approach, but Clausius¹⁵ asserted that he was wrong. A discussion ensued in which Thomson¹⁶ recognized the importance of the permeability of the medium and pointed out that the matter could be subjected to experimental test. An experiment was performed by Sargent¹⁷ but his account is brief and the outcome unclear. More recently Sommerfeld⁴ has asserted that Maxwell was in error in claiming that the force on a magnetic pole depends on H , and in his book⁵ he clearly establishes his system as factually different from the Maxwell-Kennelly approach.

Discussion still continues entirely on the basis of theoretical argument, but we have now subjected these arguments to experimental test by determining the couple on a long thin magnet immersed in a magnetic medium. The magnet was hard in the normally accepted sense that the internal state of polarization (J or M defined from (2) or (4)) was independent of the medium. If this is taken to imply that the moment of the magnet does not change on immersion in the medium, the experiment provides a test of equations (1) and (3) and can thus distinguish between the correctness of the Sommerfeld and Kennelly systems.

Fluid media are only weakly magnetic and it would be very difficult to make measurements of couples and fields with sufficient accuracy to test equations (1) and (3) directly. We therefore used a null method in which the couple on the magnet was balanced by the couple on a current-carrying coil placed in the same field; the current I for which the couple on the coil equalled that on the magnet was measured in two media of differing permeability. The couple on a current loop, completely immersed so that the medium passes through the loop, is proportional to IB —a fact that is not in dispute. Thus if the moment of the magnet is invariant and the Sommerfeld equation (3) is correct, the current I at balance will be the same for both media, whereas if the Kennelly equation (1) is correct the currents for the two media will differ by a factor equal to the ratio of the permeabilities. In this method the magnitude of the applied field and the effect of changing the

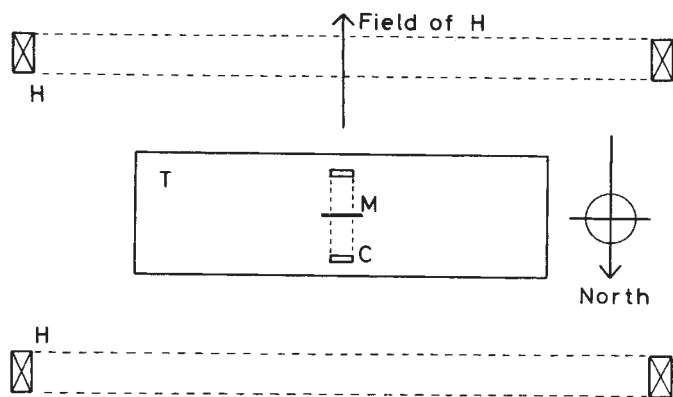


Fig. 1 Horizontal section through apparatus (approximately to scale).

medium on the magnitude of this field are unimportant. What matters is that the change of medium changes the ratio of B to H in the region of the magnet/coil assembly.

A horizontal section through the apparatus is shown in Fig. 1. The coil C had a diameter of 42 mm and was wound with 400 turns; it was suspended on a vertical phosphor-bronze torsion suspension through which its current was supplied. The bar magnet M was of length $l = 20$ mm and of square cross-section with side $a = 1.55$ mm; it was attached rigidly at the centre of C and its magnetic axis was adjusted in a preliminary experiment to be parallel to the magnetic axis of C to within about 0.002 radian. This assembly was situated at the centre of a 'Perspex' tank measuring $20 \times 20 \times 6$ cm which could be filled either with water or with a 4 M solution of MnCl_2 . An external field of approximately 180 A m^{-1} could be applied from a pair of Helmholtz coils H (diameter 31 cm) lying outside the tank; this field was parallel to the horizontal component of the Earth's field and perpendicular to the large face of the tank. In all measurements the axis of the suspended coil/magnet assembly was perpendicular to the external field as shown in Fig. 1.

With water ($\mu_r = 1.00000$) in the tank, a determination was made of the current in C such that no motion of the suspended system occurred when the field of the Helmholtz coils was switched on and off. This current was approximately 57 mA and was determined to an accuracy of about $1.5 \mu\text{A}$. The experiment was then repeated with the MnCl_2 solution in the tank. The magnetization of a magnet varies with temperature and the temperature of the liquid was therefore measured at a point close to the magnet. The currents at balance were determined at three temperatures in each medium; the results are plotted in Fig. 2 and parallel lines have been drawn through the two sets of points. At a given temperature the balancing current is different for the solution and for water, and their ratio was found to be 1.00065 ± 0.00005 . The relative permeability of the liquid measured by Quincke's method was 1.00067 ± 0.00002 .

The magnet was a bar of Magloy 2 (supplied by the Plessey Company Ltd), magnetized in an electromagnet and stabilized by applying a reverse field to reduce its magnetic polarization at zero field by about 10%. After removal from the electromagnet, its moment (in Kennelly units) was $4.0 \times 10^{-8} \text{ Wb m}$; in this state the polarization was non-uniform, with an average value of about 90% of its uniform value before removal from the electromagnet. It is necessary to establish that the magnet was "hard" in the sense that changes in its polarization on immersion in the MnCl_2 solution could be neglected. These changes occur because the surrounding medium modifies the demagnetizing field H at each point in the magnet, and so produces changes in the value of J at each point. As the magnet had been cycled several times between air and the MnCl_2 solution before the start of the experiment itself, further changes of this type corresponded to moving the working points of all portions of the magnet along the appropriate

recoil lines in the J - H diagram. Considering axial components, the change in J for a change δH in H will then be $(\mu_{\text{rec}} - 1)\mu_0\delta H$, where μ_{rec} is the recoil permeability, given by the manufacturers as approximately 3.8. In changing the surrounding medium from a medium of relative permeability 1 to one of slightly greater relative permeability μ_r , the maximum fractional change that can be produced in H at a point inside the magnet is $-(\mu_r - 1)$. The maximum fractional change in the magnetic moment of the magnet is therefore

$$-(\mu_r - 1)(\mu_{\text{rec}} - 1)\mu_0 \frac{\int H dV}{\int J dV}$$

where the integrals are evaluated over the volume of the magnet; equation (5) has been assumed to be valid. An upper limit to $\int H dV$ can be estimated by calculating the field H at points on the axis of a uniformly polarized bar and imposing the condition that the value of H near the ends cannot exceed the coercive field of the material ($6.2 \times 10^4 \text{ A m}^{-1}$). Such calculations show that the fractional increase in the magnetic moment of the magnet on immersing it in the MnCl_2 solution is not more than 0.07 ($\mu_r - 1$). The change in the current in the suspended coil produces a change in its field at the magnet but the ensuing fractional change in moment is only 0.003 ($\mu_r - 1$). Within the limits of the error of this experiment the magnet may therefore be taken to be hard.

It was implicitly assumed in the description of the underlying theory of the experiment that the magnet and the coil were situated in a uniform field so that the same field acted on them. In practice the applied field was not perfectly uniform so that, even *in vacuo*, the effective field acting on the magnet differed from that acting on the coil. We are concerned only with the change in the balancing current I produced by the presence of the medium and the important matter is therefore the way in which the small field produced by the polarization of the medium modified the degree of inhomogeneity of the original Helmholtz field. The size of this effect was computed, using experimentally determined values for the profile of the Helmholtz field and taking into account the finite size of the tank of liquid used, but errors from this source were found to be negligible.

The experiment shows that the ratio of the balancing current when the system is immersed in the MnCl_2 solution to that when immersed in water is, within experimental error, equal to the reciprocal of the relative permeability of the solution. The ratio of the balancing currents is definitely not unity. If we take the moment of the magnet to be independent of the surrounding medium, this result is consistent with the Kennelly

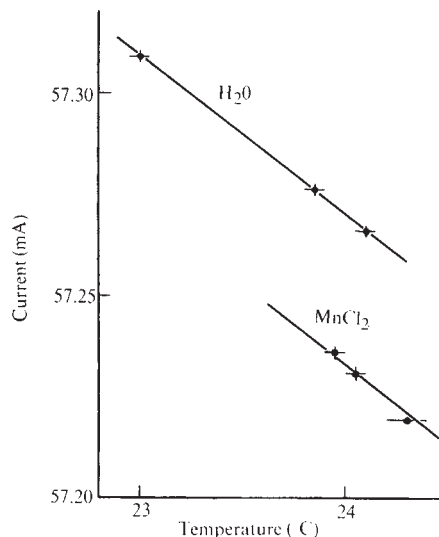


Fig. 2 Balancing current in coil as a function of temperature.

equation (1) and not with the Sommerfeld equation (3). Allowance for any change in the moment of the magnet due to insufficient hardness could not reverse this conclusion because the effect does not have the required sign. We therefore conclude that the couple on a long thin hard magnet which has a constant magnetic moment $\mathbf{j}$ is given by the Kennelly equation

$$\mathbf{T} = \mathbf{j} \times \mathbf{H}$$

This equation applies to a long thin magnet, which is the system that comes most naturally to mind when thinking of a "dipole". In general, however, the couple on a magnet in a medium will depend on its shape. For a disk-like magnet magnetized perpendicular to its plane with a magnetic moment $\mathbf{j}$ (defined from (5)), the couple in the Kennelly system is given by

$$\mathbf{T} = \mathbf{j} \times \mathbf{B}/\mu_0 \quad (9)$$

The corresponding equations for electrically polarized matter are:

$$\text{needle shape: } \mathbf{T} = \mathbf{p} \times \mathbf{E} \quad (10)$$

$$\text{disk shape: } \mathbf{T} = \mathbf{p} \times \mathbf{D}/\epsilon_0 \quad (11)$$

It is not possible simply to say that the experiment shows that equation (1) is correct whereas equation (3) is false for, as has already been indicated, these equations can be treated as definitions of the moments $\mathbf{j}$ and $\mathbf{m}$. If this is done, the experiment shows that $\mathbf{j}$ is invariant on immersion in a magnetic medium, whereas $\mathbf{m}$ is not. This is contrary to the position adopted by Sommerfeld who states that his measure of dipole moment is conserved whereas the Kennelly measure is variable (ref. 5, pages 41 and 87—the statement is actually formulated in terms of poles). Any attempt to formulate a system of electromagnetism based on equations (3) and (4) necessarily involves abandoning equation (6). This is not generally recognized by users of the Sommerfeld system; the *International Electrotechnical Vocabulary*⁶, for example, defines the "moment magnétique ampèrien d'un aimant" by equation (3) and adds a statement which appears equivalent to (6); but it is hard to believe that they are advocating the abandonment of equation (4).

We are led to the conclusion that any system in which the couple on a magnet is written as $\mathbf{m} \times \mathbf{B}$ is misleading, and the full system of electromagnetism as formulated by Sommerfeld⁵ is in error. Sommerfeld's system has, however, sometimes been incorrectly stated and, although Sommerfeld's equations are correctly stated in the review by Smith¹⁴, the report of the Coulomb's Law Committee¹⁸ has caused much confusion by attributing to Sommerfeld a system of equations which is not his^{1,2}. In particular, equation (3) is replaced by $\mathbf{T} = \mu_0 \mathbf{m} \times \mathbf{H}$ or its equivalent. This removes the factual error but makes the system non-Sommerfeld in character even though the units of magnetic moment are the same as those appropriate to Sommerfeld's system. Once it is recognized that systems which use equation (3) are unacceptable, there remain several possible systems which differ from the Kennelly system only in matters of convention regarding the places at which μ_0 is introduced. The system developed by the Coulomb's Law Committee and wrongly attributed to Sommerfeld is one of these alternatives. The problem is more complex than a choice between "Kennelly units" and "Sommerfeld units" for the mere specification of units leaves ambiguity about the equations and quantities intended.

We do not intend to draw deep theoretical conclusions nor to discuss the relative merits of the alternative systems of equations that are physically correct. One immediate consequence of the experimental result is, however, evident when equation (1) is compared with equation (10) and equation (9) with equation (11). If there is a dualism between electric quantities and magnetic quantities in the macroscopic theory of electromagnetism, then the magnetic field corresponding to the $\mathbf{E}$ -field is the $\mathbf{H}$ -field and not the $\mathbf{B}$ -field. It can be shown

that there is such a dualism; it is seen clearly in the tensor formulation of the special theory of relativity.

It is, of course, often convenient to refer to the magnetic moment of a current loop. If this is defined by $\mathbf{m} = \mathbf{IA}$ or $\mathbf{j} = \mu_0 \mathbf{IA}$ the appropriate equations for the couple on such a loop are equations (3) and (9) respectively. A coil which is permeated by the ambient medium responds to the $\mathbf{B}$ -field whatever its shape but a coil with an evacuated core behaves like a magnet of the same shape; this is a consequence of the Ampèrian theory of the magnet.

The conclusions of this paper can be reached from the basic concepts of electromagnetism and, indeed, many authors have done this. Nevertheless the importance of the $\mathbf{B}$ -field in problems of current electricity has led many others to incorrect conclusions. The subject is of immediate importance because of the danger that decisions about standardization of systems may be taken in the belief that only matters of convention need be considered. We have set out to demonstrate that matters of physical fact are involved, and we hope that the introduction of an experimental result into the discussion will be a helpful clarification.

The general secretary of the International Electrotechnical Commission has asked us to state that the chairman of the IEC Technical Committee No. 1, Terminology, which is responsible for the *International Electrotechnical Vocabulary*, is aware of the problem and that the points raised in this communication will be considered in the work of revision which is now taking place.

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Algorithm for the Production of Contour Maps from Linearized Data

COLE has proposed an algorithm which produces a generalized surface for contouring scattered data¹. The algorithm works well when the data points are randomly distributed but improbable results have been obtained when the data points are distributed along lines. There are two reasons for this: one is the extrapolations which occur into regions without data and the other is the generation of unlikely gradients

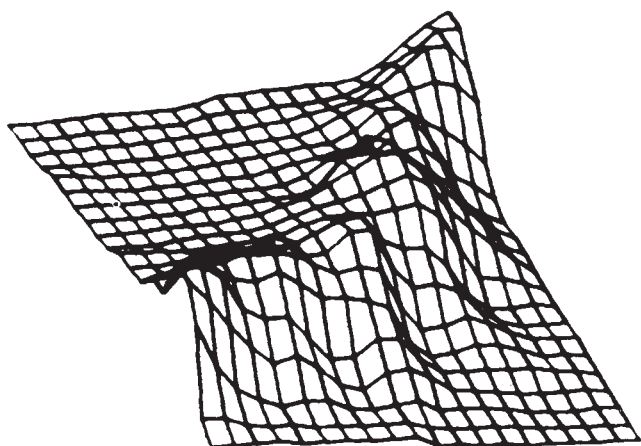


Fig. 1 A perspective grid derived from a matrix of values computed from linearized measurements.

across the lines. Measurements of many geophysical properties, made by moving vehicles, ships and so on, are often distributed along lines which are not necessarily straight. They may cross one another but the distance between adjacent measurements on the lines is usually much less than the distance between the lines. Such a distribution of measurement points may be found in other situations where the two dimensions are not spatial.

By Cole's method, the generalized surface is actually a matrix of Z values and the initial values of the matrix elements are derived from a global least squares fit of a second-order two-dimensional polynomial function. This global surface is then modified by a local least squares quadratic fit involving the 3 by 3 matrix around each data point. The modified matrix is then smoothed by means of an algorithm which removes discontinuities of gradient between the global and local surface but does not affect quadratic surfaces. The algorithm is made iterative by using the matrix obtained as the new global surface for a repeat of the process. The effect of this is the production of a smooth surface which passes through the data points. In areas where data are absent, the algorithm tends to extrapolate first and second derivatives. In practice this may be undesirable. Imagine a string of data points passing over a hill in the measured property. If the path deviates slightly from a straight line as it crosses the hill, this would be interpreted as a steep slope perpendicular to the track. But this would not be the subjective evaluation of the data, because such steep slopes are not found along the path of measurement. When the source data are linearized, more information is available about the statistical nature of the surface. I have therefore modified Cole's algorithm to improve these two aspects—the extrapolation of first and second derivatives, and the use of the statistical information. It is necessary to specialize somewhat because I propose that on a large scale neither the first nor second derivatives of the measured property can be extrapolated indefinitely. Instead, in any areas without data, we may expect a horizontal plane: this is true for many geophysical measurements but may not be valid for other types of property. Bearing this in mind, each element of the initial matrix of Cole is set equal to the value of the nearest data point. Then a single data point yields a single-valued plane, and at points away from the data the resultant surface tends to the value of the nearest data point. In this way improbable cross track gradients are not generated because initially the matrix values at either side of the track are equal to the value on the track, although there will in general be discontinuities between tracks. If the property being contoured has known discontinuities within the area of the matrix, in particular if there is a boundary

(such as a known coastline) beyond which contours should not be plotted, then any data from beyond the boundary are omitted (the survey is discontinued at the boundary) and, after contouring, the plane surface which will extend beyond the boundary into the area of no data is omitted. The local quadratic least squares fit of Cole has been retained because on a small scale these extrapolations are permitted. The principal change to Cole's algorithm is in the smoothing. The source data are scanned along the survey lines and the root mean square gradient between adjacent data points is determined. We may now assume that the function which has been measured has statistical properties which are isotropic. To be more specific, I assume that the mean square gradient observed along the track is the same as that expected across the track. We may therefore smooth the matrix obtained by an amount which increases rapidly for gradients greater than the r.m.s. gradient determined along the track. The gradient in the vicinity of each matrix point is found, and the Z value changed by an amount $\Delta Z a/(1+a)$ in such a way as to reduce the gradient; a is the ratio between the local gradient and the r.m.s. measured gradient. Thus a matrix is produced representing a surface which passes through the data points and has the same statistical properties as the source data. This method is only possible because the data are distributed along lines, and it is not suitable for randomly scattered data. The matrix obtained is then contoured by a standard computer routine to produce a contour map. Alternatively, it is worth considering a perspective grid as shown in Fig. 1.

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Distance between Sets

DISTANCE functions expressing the degree of dissimilarity of sets have found use in physical anthropology¹, psychology², numerical taxonomy³, ecology³ and elsewhere. During an ecological study by one of us, it was noticed that the similarity coefficient of Jaccard⁶, used in ecology, gives rise to a metric function satisfying the triangle inequality. For two non-empty finite sets X , Y , the Jaccard coefficient is the number of elements in the intersection $X \cap Y$ of X and Y . This coefficient

$$r = \frac{|X \cap Y|}{|X \cup Y|}$$

(we use absolute value signs to indicate number of elements) has a heuristic interpretation. It measures the probability that an element of at least one of two sets is an element of both, and thus is a reasonable measure of similarity or "overlap" between the two. The one-complement

$$d(X, Y) = 1 - r(X, Y) \quad (1)$$

may then be considered a measure of the dissimilarity of the two sets.

To study patterns of similarity or relatedness of sets of data, it is often helpful to represent them abstractly as points in a space, which can be studied by the methods of cluster analysis or ordination. For this, it is an advantage if the measure of dissimilarity has the formal properties of a metric or distance function.

If X , Y and Z are non-empty finite sets, we claim that

$$d(X, Y) + d(Y, Z) \geq d(X, Z) \quad (2)$$

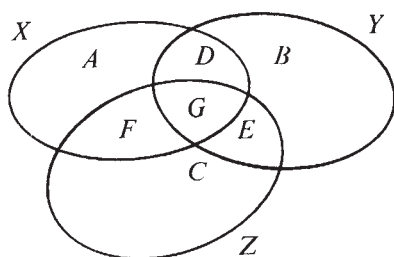


Fig. 1 Representation of sets and subsets.

By the definition of the function d , this reduces to showing that

$$\frac{|X \cap Y|}{|X \cup Y|} + \frac{|Y \cap Z|}{|Y \cup Z|} \leq \frac{|X \cap Z|}{|X \cup Z|} + 1 \quad (3)$$

We break up $X \cup Y \cup Z$ into seven disjoint subjects A to G which we use to transform inequality (3) into a manageable form. Thus

$$X \cup Y \cup Z = (A \cup B \cup C) \cup (D \cup E \cup F) \cup G$$

where

$$\begin{aligned} A &= X - (Y \cup Z), \quad B = Y - (X \cup Z), \quad C = Z - (X \cup Y), \\ D &= X - (A \cup Z), \quad E = Y - (X \cup B), \quad F = Z - (C \cup Y), \\ G &= X - (D \cup F \cup A) = Y - (D \cup E \cup B) + Z - (E \cup F \cup C) \end{aligned}$$

This is best understood from Fig. 1.

If $a, b, c, \dots$ denote the number of elements in the corresponding sets $A, B, C, \dots$, the inequality (3) becomes

$$\frac{d+g}{v-c} + \frac{e+g}{v-a} \leq \frac{f+g}{v-b} + 1 \quad (4)$$

where $v = a + b + c + d + e + f + g$, the number of elements of $X \cup Y \cup Z$. Symbolically written, the inequality (4) becomes

$$\frac{d'}{c'} + \frac{e'}{a'} \leq \frac{f'}{b'} + 1$$

or

$$a'b'd' + b'c'e' \leq a'c'f' + a'b'c'$$

or

$$(v^2 - av - bv + ab)d' + (v^2 - bv - cv + bc)e' \leq (v^2 - av - cv + ac)f' + (v^2 - av - bv + ab)c'$$

This inequality is equivalent to $0 \leq v^3$

$$\begin{aligned} &+ v^2(-a-b-c-d-e+f-g) \\ &+ v[ab+ac+bc+ad+bd+be+ce+2bg-af-cf] \\ &+ \{-abc-abd-abg-bce-bcg+acg+acf\} \end{aligned} \quad (5)$$

The second term is equal to $v^2(2f-v)$ so that the sum of the first two terms is $2fv^2$. The inequality now, symbolically, is

$$0 \leq v(2fv + [\dots]) + \{\dots\}$$

Because $v = a + b + c + d + e + f + g$ the two negative terms of $[\dots]$ cancel with terms in $2fv$. And the negative terms of $\{\dots\}$ cancel with terms in $v[\dots]$, namely with terms of the part

$$a(bc+bd+2bg)+b(ce)+c(2bg)+d0+e0+f0+g0$$

of $v[\dots]$. Because all negative terms on the right side of inequality (5) cancel, the inequality is established.

$d(X, Y)$ satisfies the triangle inequality (2) and is also positive definite ($d(X, Y) = 0$ if and only if $X = Y$) and symmetric ($d(X, Y) = d(Y, X)$), so it has the properties of a metric function in a space, the elements of which are finite non-empty sets. The argument presented does not depend essentially on the finiteness of the sets, and the theorem may be generalized by introduction of a suitable measure function for infinite sets.

We have not yet found a simpler or more elegant proof of this theorem based on the theorems of set-algebra. The absence of, or difficulty of finding, such a proof may explain the novelty of the result.

The function d is related to another metric function

$$d'(X, Y) = |X \cup Y - (X \cap Y)|$$

where $X \cup Y - (X \cap Y)$ is the symmetric difference of X, Y in that

$$d = \frac{1}{|X \cup Y|} d'$$

for non-empty finite sets X, Y, d' , in turn, is a constant times the one-complement of a well-known measure of similarity, the simple matching function

$$r' = \frac{|X \cap Y| + |\overline{X \cup Y}|}{|X \cup Y|}$$

The properties of d and d' are, however, quite different, as one might expect from the probabilistic quality of d in ranging from 0 to 1. The probabilistic and geometric features induced by d are the subjects of further study.

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BIOLOGICAL SCIENCES

Specific RNA Methylase associated with Avian Myeloblastosis Virus

At least three enzymes of DNA metabolites are found in the RNA tumour virus group—an RNA dependent DNA polymerase^{1,2}, a DNA dependent DNA polymerase³ and an endonuclease⁴. We now report that a specific RNA methylase is associated with the avian myeloblastosis virus (AMV) which transfers a methyl group from S-adenosylmethionine to certain guanine bases in RNA to give N²-methylguanine.

There is linear incorporation of the methyl group of S-adenosylmethionine by virus from a high-speed pellet which depends on the addition of both surfactant and tRNA (Fig. 1). There is, however, an appreciable time-dependent background, which does not represent incorporation into endogenous nucleic acid bases, nor does it seem to decrease when rate-zonal purified virus is compared with the high-speed pellet from viraeic plasma. Because this background represents almost one-third of the measured incorporation, we have devised a column assay to isolate and identify the major radioactive nucleic acid components formed in the reaction.

The major radioactive peak in the column assay consists solely of N²-methylguanine as identified in six thin-layer chromatography solvents (including isopropanol-HCl-water,

68:17.6:14.4, and n-butanol-water-ammonium hydroxide, 86:14:1) and ion exchange on 'Dowex 50' resin with known methylated bases (Fig. 2). The major nucleic acid hydrolysis products in this column assay elute in the following order: uridylic acid, cytidylic acid, guanine and adenine.

A comparison of the N^2 -guanine methylase activity in virus from a high-speed pellet with the activity of rate-zonal purified virus from the same sample of viraemic plasma is shown in Table 1. There is only a modest increase in specific activity, which probably results from the high concentration of virus existing in the high-speed pellet; most cellular contaminants are removed by the previous centrifugation at 10,000g for 15 min. If methylase activity were adventitiously present, perhaps trapped in membrane vesicles formed from cell fragmentation, there should be a significant decrease in specific activity because there is considerable purification of AMV from these components by rate-zonal centrifugation. Our result therefore suggests that the enzymatic activity is associated with the virions. Table 1 also shows that the methylase activity is: (a) stable after multiple freezing and thawing in standard assay buffer; (b) destroyed by heating at 100° C for 3 min in standard assay buffer; (c) zero with *E. coli* DNA

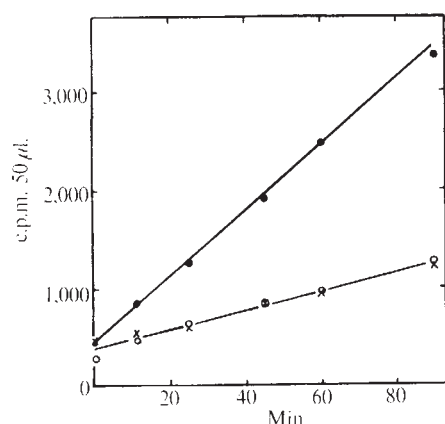


Fig. 1 Enzyme assay. The standard assay buffer contained 50 mM Tris HCl, pH 8.3, at 37° C, 60 mM NaCl, 16 mM magnesium acetate, 30 mM dithiothreitol. The incubation volume was 0.2 ml. containing 400 µg tRNA (*E. coli* B), 2.5 µCi S-adenosylmethionine-methyl- 3 H (New England Nuclear Corp., specific activity 3.28 Ci/mmol) and 0.4 mg to 0.8 mg virus protein (Lowry procedure). The virus was disrupted by preincubation with 0.75% v/v 'Sterox SL', a nonionic surfactant (Monsanto Co.) in standard buffer at 0° for 15 min and an equal volume of the virus solution was added to the incubation solution to start the reaction. The radioactive incorporation was assayed by the filter paper technique of Mans and Novelli⁷, in which the hot trichloroacetic acid extraction was omitted. ●, Complete incubation; ×, minus tRNA; ○, minus surfactant.

Fig. 2 Analysis of 3 H incorporation by hydrolysis and ion exchange chromatography. A sample of 2 ml. of 1 M Tris-HCl, pH 8.5, and 4 mg of carrier tRNA was added to the incubation solution and then precipitated in the cold with 1 ml. of 50% trichloroacetic acid. After centrifugation the pellet was suspended in 2 ml. of 1 M Tris-HCl and stirred for 20 min at room temperature. Undissolved material was removed by centrifugation and the supernatant was precipitated as above four times. After the final precipitation had been hydrolysed in 3 ml. of 1 N HCl at 97°-99° C for 30 min, it was applied to a 'Dowex 50-H⁺' column (1 cm × 7 cm) equilibrated with 1 N HCl. Gradient elution was accomplished by mixing 2 M ammonium acetate with 125 ml. of 1 M acetic acid in a closed flask. Fractions containing 1.4 ml. were collected each 10 min, monitored at 260 nm and counted in 15% 'Biosolve'-toluene solution. ●, A_{260} ; ×, 3 H in complete incubation; ○, 3 H in incubation minus tRNA.

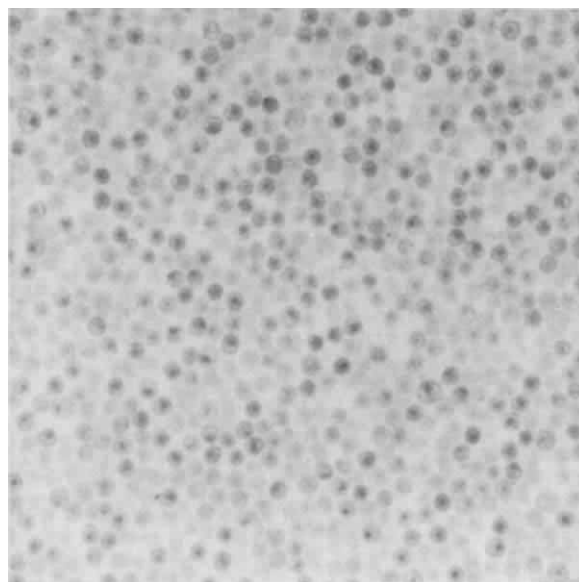


Fig. 3 Thin section electron micrograph of rate-zonal purified AMV. ($\times c. 20,000$.) Viraemic plasma (from leukaemic chicks in which by microleucocrit at least 20% of the blood volume consisted of myeloblasts) was centrifuged at 5,000g for 15 min (low speed) and the supernatant solutions were pooled and centrifuged at 10,000g for 15 min (intermediate speed spin). Aliquots of this supernatant plasma were then layered on 'Ficoll' gradients (5%-25%) in the standard virus purification buffer (0.1 M NaCl, 1 mM EDTA sodium salt, and 50 mM Tris-HCl, with final pH of 7.4 at 0° C), and centrifuged at 25,000 r.p.m. for 55 min in 5/8 × 4 inch buckets in an SW27 rotor. The dense virus band below the 'Ficoll'-plasma interface was removed with a syringe by needle puncture, the pooled bands were diluted twice with standard buffer and centrifuged at 40,000g for 60 min. The resulting rate-zonal purified pellet was suspended in the methylase assay buffer. If the 'Ficoll' centrifugation procedure was omitted, the supernatant after the intermediate speed spin was pelleted by centrifugation at 40,000g for 60 min to give a high-speed pellet which was resuspended in the standard assay buffer. Note the absence of nonviral material.

(200 µg, heat denatured); and (d) only one-eighth the amount of acceptance of methyl groups by an equivalent amount of brewer's yeast tRNA in the same conditions. Data from experiments not presented here indicate that the methylase activity is released by 'Nonidet-P40' (0.25% v/v), and that concentrations of 'Sterox SL' as high as 1% v/v do not cause inhibition of activity.

Fig. 3 is an electron micrograph of a typical preparation of rate-zonal purified AMV which shows the purity. Although only briefly described here, a more detailed report of this purification procedure will be published shortly (K. Stromberg, in preparation).

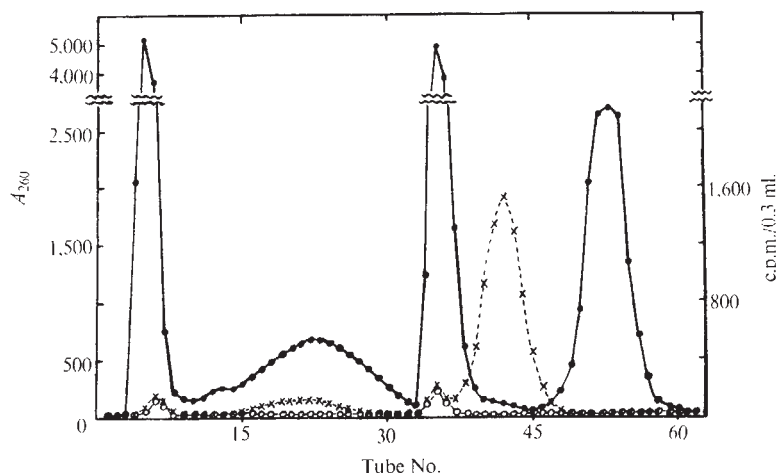


Table 1 Response of Methylase Activity to Various Conditions

	Total c.p.m./h in N ² -methylguanine	Specific activity of methylase: c.p.m./mg protein/h
High-speed pellet virions:		
Complete incubation	19,300	24,400
Minus tRNA	0	
Frozen three times	20,800	26,300
Frozen five times	19,400	24,500
Plus yeast tRNA	2,520	3,180
Plus DNA	0	
Heat treated	0	
Rate-zonal purified virions:		
Complete incubation	17,620	28,900
Minus tRNA	0	

More than 90% of the detectable methylase activity is specific for N²-methylguanine. Though this apparent specificity suggests that the activity might be an important function for the virus, complications are introduced by the complexities of the methyl acceptor (for example, unfractionated tRNA) and the variety of different conditions required for optimum activity of the various methylases⁵. As well as the possibility that this enzyme is important in the virus life cycle, its association with an oncogenic virus suggests a possible connexion with the aberrant methylation hypothesis of malignancy proposed by Srinivasan and Borek⁶. In this regard, it would be valuable to examine other RNA tumour viruses for a specific RNA methylase activity.

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Changes in Hepatic Nuclear DNA-dependent RNA Polymerase caused by Growth Hormone and Triiodothyronine

WHEN hypophysectomized rats are given growth hormone or triiodothyronine, the rate of RNA synthesis is accelerated, followed by that of protein synthesis and a resumption of growth^{1,2}. The two hormones apparently affect the pattern of hepatic RNA synthesis in different ways^{3,4} and we have now found that the two hormones affect the multiple RNA polymerases of isolated nuclei in different ways.

The existence of more than one RNA polymerase activity in isolated nuclei, involving the synthesis of ribosomal and non-ribosomal RNA, was inferred from experiments in which nuclei were incubated in high and low concentrations of salt⁷. After chromatographic separation^{5,6} the enzymes have the ionic requirements for ribosomal (nucleolar) or non-ribosomal (nucleoplasmic) RNA formation. We have also made use of

the ability of the fungal toxin α -amanitin to inhibit selectively the nucleoplasmic RNA polymerase activity^{8,12}.

Male Sprague Dawley rats (90–110 g) were hypophysectomized and maintained on standard laboratory chow supplemented by salt and sucrose. Seven and eight days later they were given either a single subcutaneous injection of 3,3',5-triiodo-L-thyronine, 20–22 h before death, or received bovine growth hormone (from the National Institutes of Health, Bethesda) or human growth hormone (International Standard, National Institute for Medical Research, Mill Hill) 12 and 3 h before death, respectively. Nuclei were prepared from liver by differential centrifugation and their capacity to form RNA was measured *in vitro*^{7,13}. The DNA-dependent RNA polymerases were isolated by chromatography on 'DEAE Sephadex'^{5,6}. Enzyme activity was assayed and fractions corresponding to different peaks were pooled. Protein was assayed by the filter paper technique with xylene brilliant cyanin G staining¹⁴.

The choice of the time of subsequent analysis was predicated from the results of previous experiments showing changing RNA polymerase activities and not necessarily maximal stimulation. In this way we hoped to select for the early responses to the hormone action. In the initial experiments RNA polymerase was measured in whole nuclei at low and high ionic strength and in the presence or absence of α -amanitin. There was significantly greater inhibition of ATP incorporation by α -amanitin at high than at low ionic strength with both control and hormone-treated animals; however, after injection of growth hormone, there was a significant reduction in inhibition of the enzyme assayed at low ionic strength (Table 1). The amanitin-insensitive enzyme is the more active when nuclei are assayed at low ionic strength with a preponderant synthesis of ribosomal RNA. The decreased inhibition by amanitin after treatment with growth hormone suggested more activity or a greater quantity of this type of enzyme, but did not indicate whether a change had occurred in the amanitin sensitive enzyme. Triiodothyronine enhanced sensitivity to α -amanitin assayed at low ionic strength. This observation is difficult to assess; it may indicate a greater representation of the "nucleoplasmic" enzyme in the conditions of assay.

The elution profile of enzymatically active fractions isolated from nuclei of liver from hypophysectomized animals resembles that from normal rat liver and consists of three separate peaks of activity (Fig. 1a). The first peak eluted from the column (peak A) has been observed before it is eluted after the bulk of the protein, with the 0.1 M ammonium sulphate buffer wash, and is probably a complex mixture of proteins including RNA polymerase enzymes. Preliminary observations show that it is insensitive to rifamycin; inhibited by 3–5% by α -amanitin (2 μ g/ml.), at which concentration the activity of the second peak (B) is inhibited by 3% and that of the last major peak (C) inhibited by 90%; possesses DNAase-like activity towards

Table 1 Differential Inhibition by α -Amanitin of Stimulation of RNA Polymerase in Whole Nuclei by Growth Hormone and Triiodothyronine administered to Hypophysectomized Rats

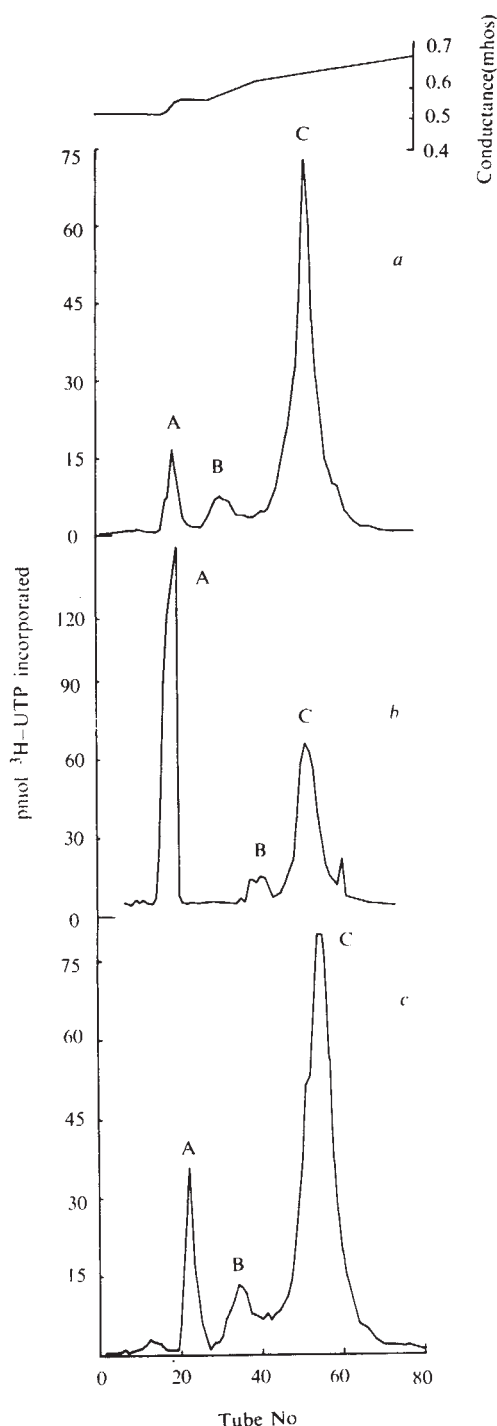
Treatment	0.3 M (NH ₄) ₂ SO ₄ added	Incorporation of ATP (μ mol/mg DNA/10 min)	% inhibition by α -amanitin
None	—	193	17
	+	305	69
200 μ g BGH; 10 h	—	237	10
	+	536	63
20 μ g T ₃ ; 22 h	—	229	29
	+	412	68

Nuclei were isolated from livers of three rats following administration of 0.15 M NaCl (control) or hormone as indicated. The nuclei were incubated as described⁷ in the presence or absence of added ammonium sulphate. Each experiment was repeated at least twice. The α -amanitin concentration was 2 μ g/ml.

Table 2 Specific Activities and Hepatic Concentrations of DNA-dependent RNA Polymerase isolated from Nuclei of Control (Untreated) and Hormone Treated Hypophysectomized Rats

Enzyme	Hypex	Incorporation of ^3H -UTP (nmol/mg protein/30 min)				μg protein/g wet weight liver			
		% inhibition by α -amanitin	Hypex+ HGH	% inhibition by α -amanitin	Hypex+ T_3	% inhibition by α -amanitin	Hypex	Hypex+ T_3	Hypex+ HGH
A	1.02	3	0.985	3	1.83	4	35.7	47.0	128.0
B	0.967	3	0.900	0	1.15	5	31.4	24.8	46.0
C	42.0	95	36.0	97	27.4	92	6.77	7.70	6.30

Nuclei were isolated from 30–35 g (six to eight rats) of rat liver following 0.15 M NaCl or hormone treatment as indicated in the text. RNA polymerase was isolated by a modification of the method described by Roeder and Rutter⁵ and after overnight dialysis was applied to DEAE-'Sephadex' columns. The various enzymes were eluted with 0.1 M $(\text{NH}_4)_2\text{SO}_4$, 0.05 M Tris pH 7.4, 5 mM MgCl_2 , 0.5 mM dithiothreitol, 0.1 mM EDTA, 20% glycerol wash followed by a 0.1–0.5 M $(\text{NH}_4)_2\text{SO}_4$ gradient in the same buffer. The column eluate was assayed as indicated in Fig. 1. The peaks of activity were reassayed and pooled. Protein concentrations and content and α -amanitin sensitivity were determined on each enzyme peak. Each experiment was repeated at least twice, and each determination was carried out in triplicate. The α -amanitin concentration was 5 $\mu\text{g}/\text{ml}$.



adenovirus DNA and no lytic activity towards bacterial 16S ribosomal RNA or to polyadenylic acid (unpublished results of E. A. S. and W. C. Russell). There is a significant and selective change in the properties of this fraction following hormonal treatment.

Triiodothyronine did not change the elution profile pattern of peaks B and C, nor their sensitivity towards α -amanitin, but increased slightly the activity in peak A (Fig. 1c). After treatment with growth hormone, there was a striking increase in the activity in peak A (Fig. 1b). There was little change in specific activities of the pooled enzymes in peaks A, B and C after growth hormone treatment, but triiodothyronine increased the specific activity of A and slightly decreased that of B (Table 2). The recovery of total protein per gram wet weight of liver increased remarkably in peak A after treatment. These results are consistent with the assay of whole nuclear preparations and show that the principal change occurs in the amanitin resistant enzyme activity.

We think that these changes represent subtle hormone-specific modifications of hepatic nuclear RNA polymerase activity before an enhanced rate of protein synthesis. The nature of the enzyme activity in peak A is not clear, but administration of growth hormone is associated with significant increases in the total protein content of peak A with maintenance of its specific activity, suggesting an increased concentration of this

Fig. 1 Elution profiles of RNA polymerase isolated from the livers of (a) hypophysectomized rats, (b) hypophysectomized rats treated with human growth hormone, and (c) hypophysectomized rats treated with triiodothyronine. Nuclear RNA polymerase, isolated by a modification of the procedure described by Roeder and Rutter⁵, was dialysed overnight at 0° C against 0.05 M $(\text{NH}_4)_2\text{SO}_4$ in 0.05 M Tris (pH 7.4 at 20° C), 5.0 mM MgCl_2 , 0.5 mM dithiothreitol, 0.1 mM EDTA, 20% glycerol. After dialysis the suspension was centrifuged at 105,000g for 1 h. The clear faint yellow supernatant was applied to a 0.9×25 cm DEAE-'Sephadex' column, washed into the resin with 10 ml. of 0.05 M $(\text{NH}_4)_2\text{SO}_4$ in the same buffer (with which the bulk of the protein was eluted), followed by 10 ml. of 0.1 M $(\text{NH}_4)_2\text{SO}_4$ (which eluted a peak of enzyme activity (A), especially after growth hormone), and then with a linear 0.1–0.5 M $(\text{NH}_4)_2\text{SO}_4$ gradient. Each fraction (0.75 ml.) was assayed for ^3H -UTP incorporation with 0.8 mM ATP, GTP, and CTP, 7 μM - ^3H -UTP, 86 mM Tris (pH 8.3 at 37°), 8% glycerol, 29 μM EDTA, 140 μM dithiothreitol, mM KCl 57 120 $\mu\text{g}/\text{ml}$. calf thymus DNA, 2 mM MnCl_2 , with the ammonium sulphate concentration at elution. After 20 min of incubation at 37° C, aliquots were pipetted onto 2.4 cm No. 1 Whatman disks, which were processed by washing first in 10% trichloroacetic acid (TCA) and 1% sodium pyrophosphate at 0° C, twice in 5% TCA and 1% sodium pyrophosphate, twice with 95% alcohol, once with absolute alcohol, once with alcohol: ether (1:1 v/v), and once with ether¹⁵. The radioactivity in the dried disks was measured in 0.05% 1,4-bis (2-(4-meth-5-phenyloxazolyl)) benzene with 0.4% 2,5-diphenyloxazole in toluene in a liquid scintillation spectrometer. The efficiency of counting was 6.8% with the method employed. Conductance was measured with a Phillips conductivity meter, with values given in mmhos.

form of polymerase. The material in peak A is not homogeneous and might be the same, amanitin-resistant, enzyme which appears in peak B; hormonal treatment could have caused some of the enzyme in peak B to be eluted at a lower ionic strength. The absence of change in specific activity in peak A in the face of an increased protein content of peak A without significant changes in B suggests that more than a redistribution of the enzyme has occurred. No significant alteration in peak C activity was associated with growth hormone therapy. Triiodothyronine administration, on the other hand, enhanced both the quantity and the specific activity of peak A, the former to a very minor degree, the latter significantly. Interpretation of specific activities and enzyme yields is complicated; although recovery of enzyme activity after chromatography was of the order of 70–80% of the starting material we have not checked for possible enhanced differential enzyme extraction brought about by hormonal stimulus under identical experimental circumstances. These results indicate that treatment with growth hormone is followed by the accumulation of more amanitin-resistant enzyme with different elution behaviour from enzyme B, and that triiodothyronine enhances the specific activity of this same enzyme. Whether the altered elution properties are related to new enzyme formation, to direct hormone interaction with pre-existing enzyme, or to a functional modification of the enzyme awaits further study.

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Effect of Steroids and Dibutylryl Cyclic AMP on the Sensitivity of Haemopoietic Stem Cells to ³H-Thymidine *in vitro*

AN early action of testosterone and chemically related steroids is to increase the sensitivity of spleen colony forming units (CFU) to the cytotoxic action of high specific activity ³H-thymidine¹. This can be observed as early as 6 h after a single

subcutaneous injection of steroid. CFU of normal adult mice are generally insensitive to the killing action of ³H-thymidine²; hence the effect of steroids was interpreted as either triggering CFU from a resting (G₀) stage into cell cycle, or shortening the cell cycle of CFU.

Experimental polycythaemia, which reduces the level of endogenous erythropoietin, did not block the effect of testosterone propionate on CFU. Accordingly, it was concluded that erythropoietin was not required for the steroid action on the cell cycle of CFU.

The effect of steroids on CFU *in vivo* was observed 6 h after the subcutaneous administration of poorly soluble compounds suspended in an aqueous medium, so that the effect following absorption may be more rapid. This study was designed, in part, to determine whether testosterone given *in vitro* could increase the sensitivity of CFU to ³H-thymidine.

Adenosine-3':5'-monophosphate (cyclic AMP) is thought to act as a "second messenger" for a variety of hormone end-effects^{3,4}. While the "second messenger" concept may be applied to many of the polypeptide hormones and to catecholamines, evidence does not strongly support its application to steroid hormone action. Accordingly, steroids and cyclic AMP may produce similar biological end-effects by acting through different cellular mechanisms⁵. To test whether it might mimic any effect of testosterone on CFU, the ability of its dibutylryl derivative to change the sensitivity of CFU to ³H-thymidine was studied.

C₃H × AKR female mice served as both donors and recipients of bone marrow cells; mice were 9–11 weeks old. The steroids studied were testosterone hydrogen succinate (THS), a water soluble compound, and 5 β -dihydrotestosterone (5 β -DHT). THS was studied over a range of 2.4×10^{-14} – 2.4×10^{-6} M and 5 β -DHT at 10^{-8} M; the required amount of 5 β -DHT was added dissolved in 1 μ l. of 95% ethanol. Dibutylryl cyclic AMP was studied over a range of 10^{-14} to 10^{-6} M; as a control for dibutylryl cyclic AMP, adenosine-5'-monophosphate (5'-AMP) was studied over the range of 10^{-10} to 10^{-6} M. 5'-AMP is the principal product of the breakdown of cyclic AMP by 3':5'-mononucleotide phosphodiesterase.

Cultures of bone marrow cells (1.6 ml. 4 – 5.5×10^6 cells/ml.) suspended in Fischer medium at pH 7.4 were incubated at 37°C in a shaking water bath. From 0–2.5 h, cultures were treated with various concentrations of the agents described above; at 2.5 h, the culture volumes were increased to 2.0 ml. by the addition of 0.4 ml. of pre-warmed Fischer medium with or without 400 μ Ci of ³H-thymidine (22 Ci/mmol). After 0.5 h exposure to ³H-thymidine, the cultures were diluted approximately 1:13 with cold Fischer medium; 0.25 ml. of diluted suspension was injected intravenously into irradiated (850 rad) recipients. Groups consisted of twelve to fifteen mice. Spleen colonies⁶ were counted 9 days after transplantation. The percentage loss of CFU from cultures due to ³H-thymidine was estimated. During culture, untreated CFU do not increase their sensitivity to ³H-thymidine.

Fig. 1 shows the effect after 3 h of THS and of 5 β -DHT on the sensitivity of CFU to ³H-thymidine; both agents increased ³H-thymidine sensitivity. The effect after 3 h of dibutylryl cyclic AMP and of 5'-AMP is shown in Fig. 2. While dibutylryl cyclic AMP increased the sensitivity of CFU, 5'-AMP was relatively ineffective. The dose-response curve to dibutylryl-cyclic AMP is bell-shaped. Peak effect is seen at about 10^{-8} M; at 10^{-6} molar, however, the ³H-thymidine effect is lost.

These results indicate that, given *in vitro*, THS, 5 β -DHT, and dibutylryl cyclic AMP increase the sensitivity of CFU to the cytotoxic action of ³H-thymidine within 3 h; these agents presumably trigger CFU into cell cycle or shorten their cell cycles. Preliminary studies suggest that THS and dibutylryl cyclic AMP increase the ³H-thymidine sensitivity of CFU as early as 1 h after exposure in bone marrow cells.

The effectiveness of the testosterone derivatives in a system free of either plasma or serum strengthens the suggestion that the previously reported¹ effect of steroids on the sensitivity of

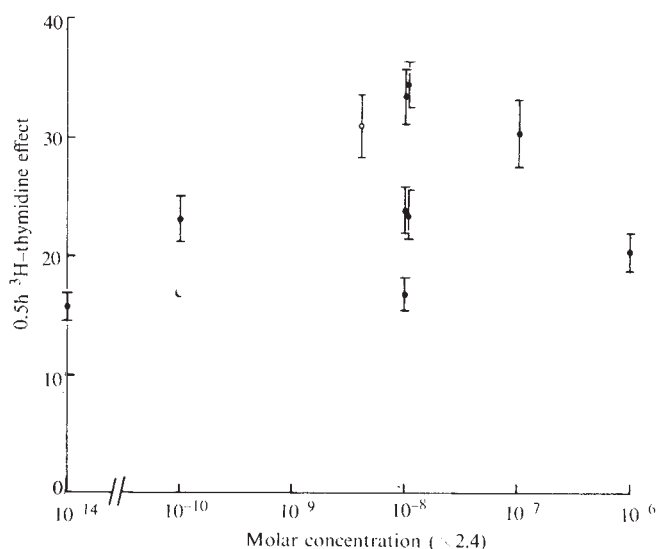


Fig. 1 Effect of testosterone on CFU *in vitro*. ●, Testosterone hydrogen succinate; ○, 5β-dihydrotestosterone.

CFU to ³H-thymidine *in vivo* does not require the presence of erythropoietin or any other plasma macromolecule. This provides support for a direct action of testosterone on bone marrow CFU; there is further confirmation for the haemopoietic activity of steroids with the 5β-H configuration⁷⁻⁹.

The mechanism of action of the testosterone on the cell cycle of CFU is not clear. Recent studies on the binding of steroids to specific cytoplasmic receptors, followed by the migration and subsequent combination of this complex with specific receptors in the nucleus⁵, offer a possible approach to this problem.

The effectiveness of dibutyl cyclic AMP within the range of physiological concentrations of cyclic AMP found in several tissues¹⁰ suggests that the adenyl cyclase system plays a role in regulating the proliferative state of CFU. This view is further supported by recent studies from our laboratory¹¹ which demonstrate that low concentrations (less than 10⁻¹² M) of isoproterenol (isoprenaline), a stimulant of β-adrenergic receptors, also act to trigger CFU into cell cycle. This effect is blocked by propranolol, a compound which specifically blocks β-adrenergic receptors. β-Adrenergic activity is closely associated with the adenyl cyclase system. The presence of such a receptor presumably on the cell surface of CFU, and the capacity of this receptor when activated to initiate DNA synthesis, argues for the regulatory role of the adenyl cyclase system. Until cell

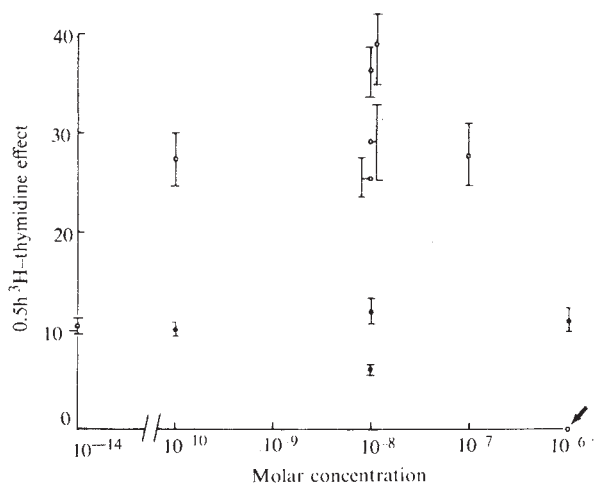


Fig. 2 Effect of cyclic AMP on CFU *in vitro*. ●, 5'-AMP; ○, dibutyl cyclic AMP.

separation techniques permit a more direct investigation of biochemical events within CFU, this suggestion must remain speculative.

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Carcinogenic Hydrocarbons and Human Cells in Culture

BOYLAND¹ has suggested that 90% of cancer in man is caused by chemicals, either endogenous or environmental. The association of human cancer with hydrocarbons dates from Percival Pott's description of chimney sweeps' cancer in 1775, greatly reinforced by the isolation 150 yr later of benzo(a)pyrene from coal tar by Kennaway² and his associates³. Although there are probably many unidentified carcinogens in soot and coal tar, the correlation between the experimental production of cancer in animals with pure hydrocarbons and the incidence of cutaneous cancer in people exposed to tar, pitch, soot, oil and similar industrial products⁴ is suggestive. It is much more difficult to assess the relevance of hydrocarbons to human cancer at other sites, and, in particular, their role in the induction of lung cancer remains unresolved.

In an earlier review⁵ of chemical carcinogenesis it was suggested that interaction with nucleic acids was of primary importance, although at that time the only evidence of a positive nature that DNA was the essential cellular receptor for carcinogenesis was the correlation reported by Brookes and Lawley⁶ between the carcinogenic potencies of a series of aromatic hydrocarbons and the extents to which these compounds were bound to the DNA of mouse skin *in vivo*. Since this time other positive correlations have been reported for alkylating agents, azo-dyes and hydrocarbons as discussed by Brookes and Dipple⁷.

For a number of carcinogens, including the aromatic hydrocarbons, covalent binding to cellular macromolecules must involve a metabolite of the carcinogen. Diamond *et al.*⁸ showed that the binding of 7,12-dimethylbenz(a)anthracene (DMBA) to the DNA, RNA and protein of cells in culture was much greater in normal rodent embryo cells than in transformed rodent cells and that this correlated both with the toxicity to, and much greater metabolism⁹ by, normal as compared with transformed cells. Andrianov *et al.*¹⁰ found that normal rodent fibroblasts metabolize benzo(a)pyrene (B(a)P) while transformed cells do not, again in agreement with the toxicity data. Duncan *et al.*¹¹ reported that although mouse embryo cells metabolize all the aromatic hydrocarbons tested, this metabolism leads to binding to cellular macromolecules only in the case of the carcinogenic compounds.

Previous studies^{12,13} with hydrocarbons and human cells have been inconclusive because either neoplastic cells, or normal cells which had been in culture for a considerable length of time, were used. Prolonged culture is known to reduce the ability to bind DMBA even of rodent embryo cells¹⁴. In the experiments reported here the effects of carcinogenic hydrocarbons on primary human embryo cells have been examined and compared with their effect on human tumour cells (HeLa).

Human embryo fibroblast cultures were prepared from lung, skin/muscle and gut tissues and tested for their ability to metabolize and bind ³H-labelled B(a)P and DMBA while similar studies were carried out with HeLa cells. In all cases the methods used were those described before¹¹.

Sterile tissue samples from 4–5 month human embryos were used to prepare lung, skin/muscle and gut fibroblast cultures (supplied by Dr H. E. M. Kay and the staff of the Foetal Tissue Bank of the Royal Marsden Hospital, London). Primary cultures were treated with ³H-B(a)P and ³H-DMBA as described previously¹¹ for mouse embryo cells. As Fig. 1 shows, both hydrocarbons were metabolized, DMBA rather more slowly than B(a)P. Calculation of the actual amount of B(a)P metabolized by the different cells in relation to the number treated gave the data of Table 1, which also includes the values obtained with cells which had been in culture for about 40 days (that is, at the tenth passage for the lung and skin/muscle cells and the seventh passage for the slower growing gut fibroblasts). It is apparent that the lung cells metabolize most efficiently and retain this property during subculture. On the other hand, the cells from the gut have a significantly poorer rate of metabolism after 40 days in culture.

The binding of B(a)P and DMBA to DNA, RNA and protein of the primary lung cells was determined after isolation of these cellular macromolecules. From these results (Table 2), binding indices were calculated and compared with corresponding values found previously for mouse embryo cells¹¹ (Table 3).

These results establish that in human embryo cells, the rate of hydrocarbon metabolism is similar to that in rodent embryo cells, and that at least for B(a)P, binding to macromolecules is also similar (Table 3). In the case of DMBA, the binding index, although of the same order as for B(a)P (Table 3), is significantly less than the very high value obtained previously with mouse embryo cells.

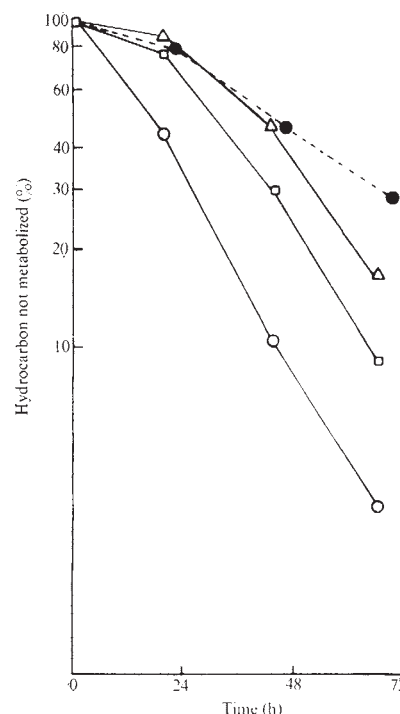


Fig. 1 The time course of metabolism of ³H-B(a)P by primary human embryonic lung (○), gut (□) and skin/muscle (△) fibroblasts, and of ³H-DMBA by primary human embryonic lung cells (●). The cell cultures were prepared by trypsinization of tissues from 4–5 month human embryos. Approximately 2×10^6 cells were plated in 4 oz medical flat bottles containing 15 ml. of Eagle's medium (MEM, Cat. No. F11, Grand Island Biological Co., New York) supplemented with 15% foetal calf serum (Flow Laboratories Ltd, Irvine, Scotland). The cells were treated 3 days later with randomly tritiated B(a)P (specific activity 5.8 Ci/mmol) or DMBA (specific activity 17 Ci/mmol) in dimethylsulphoxide (final concentration 0.5%). Metabolism was followed by extraction of 1 ml. of medium with 5 ml. of cyclohexane at zero time and subsequently, as described previously¹⁵. The initial concentration of B(a)P was 0.26 μ M and of DMBA 0.10 μ M.

Table 1 Metabolism of ³H-B(a)P by Cultures of Fibroblasts derived from Various Human Embryonic Tissues

Cell type	Number of cells per bottle		Total B(a)P metabolized (nmol)		Amount B(a)P metabolized per 10 ⁶ cells (nmol)	
	Primary culture	After 40 days in culture	Primary culture	After 40 days in culture	Primary culture	After 40 days in culture
Lung	1.9×10^6	1.8×10^6	3.8	4.0	2.0	2.2
Skin/muscle	2.9×10^6	1.3×10^6	3.3	1.7	1.1	1.0
Gut	2.0×10^6	1.3×10^6	3.6	0.75	1.8	0.58

The cells were tested after either 4 days (primary cultures) or 40 days in culture. The cells were prepared and treated essentially as described in Fig. 1. The metabolism figures given were obtained after 72 h exposure to ³H-B(a)P (0.26 μ M). The extent of metabolism was estimated as described in Fig. 1 and the final number of cells was determined by trypsinization and counting in a haemocytometer.

Table 2 Extent of Reaction of ³H-B(a)P and ³H-DMBA with Cellular Macromolecules of Primary Human Embryonic Lung Cells

Hydrocarbon	Concentration of hydrocarbon in medium (μ M)	Time of treatment (h)	% HC metabolized	Extent of binding to macromolecules	
				μ mol/mol P	μ mol/100 g protein
Benzo(a)pyrene	0.28	48	84	3.04	1.03
	0.31	48	78	3.69	3.65
7,12-Dimethylbenz(a)-anthracene	0.10	96	77	1.40	0.51
	0.10	96	82	1.66	0.44

Cells were prepared as outlined in Fig. 1 except that approximately 2×10^7 cells were plated in large flat glass bottles (Thompson bottles, Gallenkamp & Co Ltd, London) containing 150 ml. of Eagle's medium. After the time stated, cellular macromolecules were isolated and assayed for bound radioactivity as described⁸.

Table 3 Binding Indices of B(a)P and DMBA obtained with Primary Human Embryonic Lung Cells

Hydrocarbon	Binding index, $\mu\text{mol/mol P}$ (or $\mu\text{mol/100 g}$ for protein) divided by nmol/ml. metabolized					
	Human embryo lung			Mouse embryo		
	DNA	RNA	Protein	DNA	RNA	Protein
Benzo(a)pyrene	12.7	23.4	4.3	18.5	15.5	12.0
	15.4	26.8	15.2	13.0	17.0	11.0
7,12-Dimethylbenz(a)anthracene	18.2	14.0	6.6	170	130	22
	20.8	14.3	5.5	209	144	26

The binding indices represent the extent of reaction of the hydrocarbon with the particular macromolecule resulting from the metabolism of 1 nmol of hydrocarbon per ml. of medium to which the cells were exposed. They are calculated from the data of Table 2. Also given are the values found for mouse embryo cells in similar experiments.

Table 4 Metabolism and Binding of ^3H -B(a)P and ^3H -DMBA to Monolayer Cultures of HeLa Cells

Hydrocarbon	Concentration of hydrocarbon at zero time (μM)	% conversion to water soluble form at time stated				Binding index, nmol/mol P (or $\mu\text{mol/100 g}$ for protein) divided by $\mu\text{mol/ml}$. metabolized		
		Zero	24 h	48 h	72 h	DNA	RNA	Protein
Benzo(a)pyrene	0.28	Nil	48	68	82	5.4	7.1	5.7
7,12-Dimethylbenz(a)anthracene	0.17	Nil	26	35	47	18.8	15.9	5.0

The metabolism experiments were performed essentially as outlined in Fig. 1. After 72 h cellular macromolecules were isolated, the extent of hydrocarbon binding determined and the binding indices calculated as described previously¹¹.

Similar metabolism and binding experiments were carried out with monolayer cultures of HeLa cells (Table 4). As with the primary human embryo cells both B(a)P and DMBA were metabolized, but the DMBA metabolism was considerably slower. The resulting macromolecular binding as indicated by the binding indices can be compared with the values obtained with the embryo cells (Table 3). While the binding of B(a)P to DNA, RNA and protein was significantly less in HeLa cells than in primary human lung cells, the binding of DMBA was very similar in both cell types.

It has been suggested¹⁵ on the basis of detailed studies of B(a)P metabolism in mouse embryo cells that alternative pathways of hydrocarbon metabolism may exist, only one of which results in macromolecular interaction. The results discussed above could be explained if HeLa cells are defective in the enzyme system leading to binding, and studies of the pattern of B(a)P metabolites produced by HeLa as compared with embryo cells might indicate whether this is the case. DMBA binding in both HeLa and human embryo lung cells is considerably lower than that in mouse embryo cells, and this again may indicate different pathways of metabolism of this hydrocarbon by different cell types.

Preliminary experiments indicate the need for caution in interpreting toxicity data. Neither B(a)P nor DMBA affected the plating efficiency of HeLa cells over a concentration range of 0.05–50 nmol/ml. of medium, but the size of the colonies decreased with increasing dose. An effect consistent with these observations was seen when HeLa cells in suspension were treated with hydrocarbons. After 24 h in these conditions the cell number relative to control decreased with increasing hydrocarbon concentration.

This pattern of toxicity response by HeLa cells is in contrast to that found for rodent embryo cells (unpublished data) where a reduction in plating efficiency was evident at the lowest dose used (0.05 nmol/ml.) while no effect on colony size was apparent even at the highest dose of hydrocarbon (50 nmol/ml.).

It is becoming accepted¹⁶ that any agent which is of itself an electrophilic reactant or is capable of being converted to such *in vivo*, and can therefore react with nucleophiles in the cell, is a potential carcinogen. For the aromatic hydrocarbons this would seem to depend on the structure of the metabolically

produced ultimate carcinogen¹⁷ and on the ability of a particular cell to generate this species.

The data reported in Table 3 indicate that, at least for B(a)P, primary human lung cells resemble mouse embryo cells in the degree to which the carcinogen becomes bound to cellular macromolecules following metabolism. The susceptibility of the mouse to hydrocarbon carcinogenicity is well established, and a correlation between hydrocarbon–DNA binding and carcinogenic activity has been found in the mouse skin⁶. Furthermore, several reports of transformation of mouse and hamster cells in culture by hydrocarbons have appeared^{18–20} and the transformed cells have been shown to produce tumours when injected into adult animals. Our experiments suggest that the necessary conditions exist for the transformation of human lung cells by B(a)P.

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Antileukaemic and Nephrotoxic Properties of Platinum Compounds

THE antitumour properties of certain inorganic platinum compounds in mice were first reported by Rosenberg *et al.*¹ Of thirty-four compounds tested the *cis*-platinum (ii) diamminodichloride and the *cis*-platinum (iv) diamminotetrachloride had the highest activity, producing marked regression of large solid sarcoma 180 tumours in 63–100% of mice.

In the rat we have found that the *cis*-platinum (ii) diamminodichloride and the *cis*-platinum (iv) diamminotetrachloride have strong antileukaemic effects on myeloid and lymphatic leukaemias. Although their effect is accompanied by uraemia, these two compounds seem to be superior to those in clinical use in that they have no undesirable effects on the normal cells of the marrow, gonads and intestine. Their antileukaemic and nephrotoxic properties seem to be related to the molecular configuration of the platinum compounds because the *trans*-platinum (ii) diamminodichloride and the *trans*-platinum (iv) diamminotetrachloride had no effect on either type of rat leukaemia nor on the kidneys of mice, rats or marmosets.

Specific pathogen-free mice and rats (Alderley Park Colony) were used. Myeloid and lymphatic leukaemias were induced in rats by feeding them with ICI 42,464 (2-γ-chlor-β-isopropylamine) ethylnaphthalene hydrochloride. Litters less than 24 h old were injected intraperitoneally with whole blood from the dosed rats with either lymphatic or myeloid leukaemias³. After 4–6 weeks leukaemias were established in the injected newborn rats which had white cell counts of 30,000 to 110,000 cm³.

Each platinum compound was administered intraperitoneally in a ball milled suspension in dispersol. Groups of six rats with myeloid leukaemias and six rats with lymphatic leukaemias received each compound in daily doses of 2 mg/kg, 0.5 mg/kg and 0.1 mg/kg. As controls, six rats with myeloid leukaemia and



Fig. 1 Proximal convoluted tubules in rat after 5 days' treatment with 2 mg/kg *cis* (NH₃)₂PtCl₂ showing degeneration and necrosis of the epithelial cells (blood urea 145/mg%).

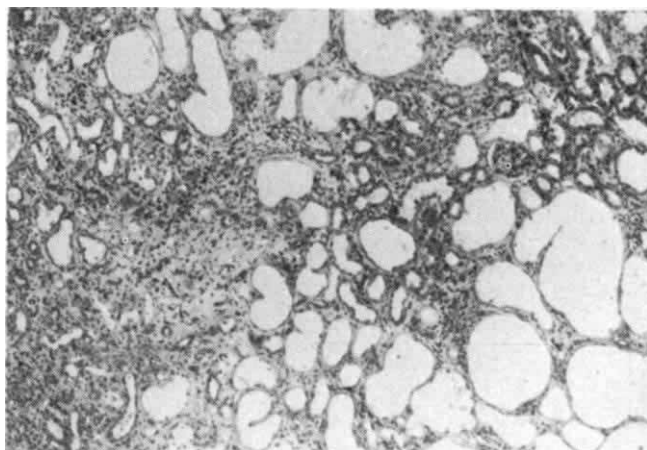


Fig. 2 Proximal convoluted tubules in rat after 5 days' treatment with 2 mg/kg *cis* (NH₃)₂PtCl₂ showing dilated tubules, atrophic epithelium, intertubular oedema and lymphocytic infiltration.

six rats with lymphatic leukaemia from the same transplanted litters were left untreated. Groups of six normal mice and six normal rats received *cis* (NH₃)₂PtCl₂, *trans* (NH₃)₂PtCl₂, *cis* (NH₃)₂PtCl₄ and *trans* (NH₃)₂PtCl₄ in daily doses of 4.0 mg/kg, 2.0 mg/kg, 1.0 mg/kg, 0.5 mg/kg and 0.1 mg/kg. Three groups consisting of two male and two female rats were given a single intraperitoneal dose of *cis* (NH₃)₂PtCl₂ at 5 mg/kg, 10 mg/kg and 20 mg/kg. Two normal male marmoset monkeys were given daily intraperitoneal injections of 2 mg/kg *cis* (NH₃)₂PtCl₂ and two normal male marmosets received 2 mg/kg daily of *trans* (NH₃)₂PtCl₂.

In normal mice and rats the *trans* (NH₃)₂PtCl₂ and the *trans* (NH₃)₂PtCl₄ produced no undesirable symptoms and the blood counts and the blood ureas remained within normal limits during the 24 days of dosing. At necropsy, histological examination revealed no abnormalities. Marmoset monkeys were unaffected by *trans* (NH₃)₂PtCl₂.

When *cis* (NH₃)₂PtCl₂ and *cis* (NH₃)₂PtCl₄ were given to normal mice and rats in a dose of 4 mg/kg a day, all animals died within 10 days; given 2 mg/kg a day, no animals survived after day 26. Haemoglobins, packed cell volumes, white cells, platelets and differential white cell counts were normal throughout the 24 days of dosing. Post mortem examinations showed the kidneys to be green and swollen and the corticomedullary regions to be congested. When examined by microscopy the kidneys showed degeneration and necrosis of the epithelium of the proximal convoluted tubules (Figs. 1 and 2). In mice and rats a renal tubular necrosis was seen in all animals dosed with 4 mg/kg and 2 mg/kg, but animals which received 0.5 mg/kg and 0.1 mg/kg did not develop a renal lesion and the blood ureas remained normal. The blood urea levels and the degree of tubular change in normal rats are shown in Table 1. Those of the mice were essentially the same. Rats given a single intraperitoneal injection of *cis* (NH₃)₂PtCl₂ at 5 mg/kg, 10 mg/kg and 20 mg/kg developed uraemia after 7–10 days (blood ureas 82, 167 and 167 mg/100 ml.) and the kidneys showed necrosis of the proximal convoluted tubules.

Marmoset monkeys given 2 mg/kg of *cis* (NH₃)₂PtCl₂ each day developed uraemia after 5–7 days (blood ureas 212 and 190 mg/100 ml.) and their kidneys showed a severe necrosis of the epithelium of the proximal convoluted tubules. Marmosets given *trans* (NH₃)₂PtCl₂ did not develop uraemia and their kidneys appeared histologically normal.

To assess possible beneficial effects of the platinum compounds on both myeloid and lymphatic leukaemias in the rat, the survival times of treated and untreated leukaemic rats and the effects on the white cell counts in the treated and untreated leukaemic rats were compared. The *cis* (NH₃)₂PtCl₂ and *cis* (NH₃)₂PtCl₄ were found to be equally effective against both myeloid and lymphatic leukaemias and the results of treating both types of leukaemia are therefore shown collectively. The

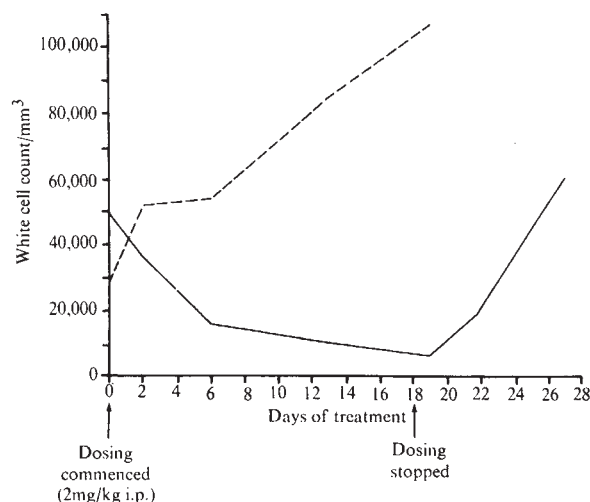


Fig. 3 Rats with myeloid leukaemia treated with *cis* (NH₃)₂PtCl₂. —, 6 treated rats; ---, 6 untreated rats.

trans (NH₃)₂PtCl₂ and *trans* (NH₃)₂PtCl₄ were found to be completely ineffective in both types of leukaemia.

Leukaemic rats given 2 mg/kg of the *cis*-platinum compounds a day had reduced white cell counts, but uraemia developed and complicated the assessment of the survival times. The optimal daily dose of both the *cis* (NH₃)₂PtCl₂ and *cis* (NH₃)₂PtCl₄ for both types of leukaemia was 0.5 mg/kg and in this dose the blood urea concentrations were not increased and the convoluted tubules were histologically normal. The therapeutic toxicity ratio seems to be approximately 1:4.

The antileukaemic effects of both the *cis* (NH₃)₂PtCl₂ and the *cis* (NH₃)₂PtCl₄ seem to be very selective because in post-mortem and histological studies of leukaemic rats treated with 0.5 mg/kg daily, cytotoxic effects on the gonads, intestinal epithelium and the kidneys were not detected. The only effect of the *cis*-platinum compounds in rats dosed with 2 mg/kg seemed to be a slight blunting of the intestinal villi.

Both the *cis*-platinum compounds had a marked effect on the white cell counts and considerably prolonged the survival times of rats with both myeloid and lymphatic leukaemias (Table 2). When treatment with *cis* (NH₃)₂PtCl₂ was discontinued in the leukaemic rats there was an immediate and progressive increase in the white cell counts (Fig. 3). In no cases can it be said that a permanent cure was obtained.

We have compared our results with those we have obtained using antileukaemic drugs for the treatment of human leukaemias (Table 3). In rats, the effects of the *cis*-platinum compounds are very similar to those of asparaginase, corticosteroids and methotrexate.

The antitumour properties of both *cis*-platinum compounds

Table 1 Effects of *cis* (NH₃)₂PtCl₂ and *cis* (NH₃)₂PtCl₄ on the Blood Ureas and Distal Convoluted Tubules of the Kidneys

Compound	Dose (mg/kg/day)	Blood ureas (mg per cent)		Effect on distal convoluted tubules
		Range	Mean	
<i>Cis</i> (NH ₃) ₂ PtCl ₂	4.0	105–240	165	+++
	2.0	105–210	140	+++
	1.0	110–185	145	++
	0.5	39– 49	42	0
	0.1	34– 49	41	0
<i>Cis</i> (NH ₃) ₂ PtCl ₄	4.0	105–280	195	+++
	2.0	115–232	180	+++
	1.0	102–190	145	++
	0.5	35– 70	44	0
	0.1	31– 40	36	0
Normal rats	Undosed	25– 70	40	0

+++ Dilatation of tubules, necrosis of epithelial cells and intertubular oedema and lymphocyte infiltration.

++ Degeneration of tubular epithelial cells but no obvious necrosis.

Table 2 Effects on the Survival Time and WBC of Dosing Rats with both Myeloid and Lymphatic Leukaemia with the Four Platinum Compounds (0.5 mg/kg daily)

Compound	Survival time (days)		Mean white cell counts/mm ³	
	Range	Mean	Before treatment	After treatment
<i>Cis</i> (NH ₃) ₂ PtCl ₂	12–48	32	64,000	4,000
<i>Trans</i> (NH ₃) ₂ PtCl ₂	2–14	6	42,000	180,000
<i>Cis</i> (NH ₃) ₂ PtCl ₄	10–34	24	82,000	11,000
<i>Trans</i> (NH ₃) ₂ PtCl ₄	4–12	9	74,000	220,000
Untreated leukaemic rats	4–18	8	30,000	110,000

Table 3 Effects on the Survival Times of Antileukaemic Compounds against Myeloid and Lymphatic Leukaemias in the Rat

Compound	Optimum dose (mg/kg)	Mean survival times (days)	
		Lymphatic leukaemia	Myeloid leukaemia
Undosed leukaemic rats	—	7	9
<i>Cis</i> (NH ₃) ₂ PtCl ₂	0.5 i.p.	30	34
<i>Cis</i> (NH ₃) ₂ PtCl ₄	0.5 i.p.	25	23
Corticosteroids (paramethazone)	0.25 s.c.	44	11
Guinea-pig serum (asparaginase)	0.5 ml. i.p.	21	9
Methotrexate	0.25 i.p.	18	14

are of considerable interest because (1) they have a marked effect on sarcoma 180 and on both myeloid and lymphatic leukaemias in the rat; (2) they are virtually free from cytotoxic effects in normal haemopoietic tissue, the gonads and the intestinal epithelium; (3) they represent a new class of inorganic antitumour compounds, one in which molecular configuration seems to be critical for an effective antitumour result, for slight molecular rearrangement abolishes the antitumour effect; (4) being relatively simple inorganic compounds the relationship of chemical structure to antitumour properties should be more easily investigated and may perhaps lead to other chemical structures with similar or better antitumour properties; and (5) the antileukaemic effect of the *cis*-platinum compound seems to be closely related to the effect on the proximal con-

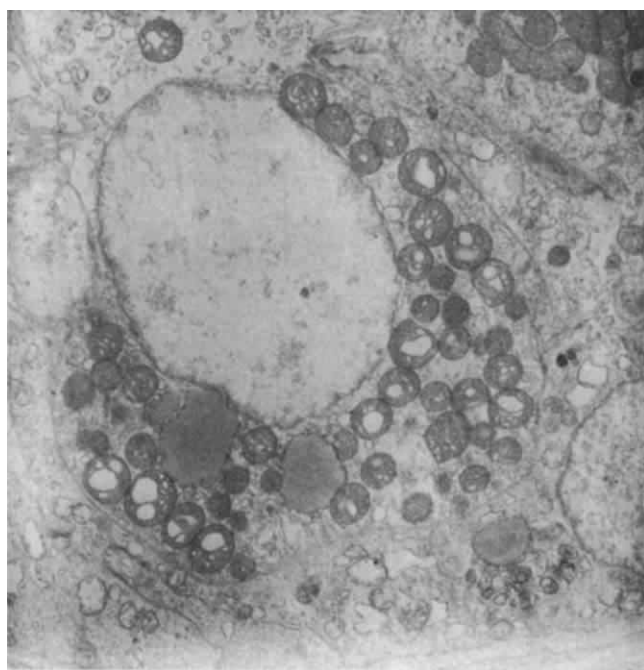


Fig. 4 Epithelial cell of distal convoluted tubule ($\times 4,500$), 48 h after a single intraperitoneal dose of 10 mg/kg of *cis* (NH₃)₂PtCl₂. The microchondrii have large vacuoles.

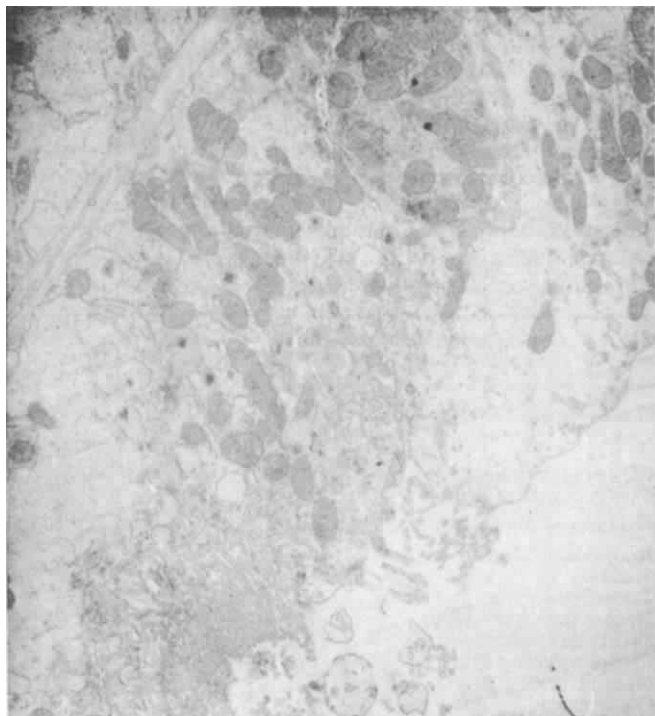


Fig. 5 Distal convoluted epithelium ($\times 4,500$) showing loss of brush border 72 h after a single intraperitoneal dose of 10 mg/kg of $\text{cis}(\text{NH}_3)_2\text{PtCl}_2$.

voluted tubules of the kidneys—both *cis*-platinum compounds have marked antileukaemic and nephrotoxic properties whereas the corresponding *trans*-platinum compounds possess neither of these properties.

The production of a necrosis of the proximal convoluted kidney tubules of rats and marmoset monkeys by *cis*-platinum compounds had not been reported before. This effect is very similar to those of mercurial compounds on man. By electron microscopy, we have tried to follow the development of the renal lesion in rats given a single 10 mg/kg intraperitoneal dose of $\text{cis}(\text{NH}_3)_2\text{PtCl}_2$. The first change, seen after 46 h, consisted of a marked vacuolation of the mitochondria of the epithelial cells of the proximal convoluted tubules (Fig. 4). This was followed after 72 h by a loss of the brush border (Fig. 5) and finally by complete disorganization and death of the tubular epithelial cells. No electron dense material suggesting platinum deposition in the tubular epithelial cells was seen.

The mode of action of $\text{cis}(\text{NH}_3)_2\text{PtCl}_2$ and $(\text{NH}_3)_2\text{PtCl}_4$ as potent antileukaemic compounds in the rat is of considerable interest, but it is not clear whether this is a direct and very selective effect on the tumour cells or whether the effect is indirect and perhaps mediated through the immunological system. The effects of $\text{cis}(\text{NH}_3)_2\text{PtCl}_2$ and $\text{cis}(\text{NH}_3)_2\text{PtCl}_4$ on rats with myeloid and lymphatic leukaemias justify a clinical trial of these compounds on human tumours and leukaemias. It seems that the most likely complication of such treatment would be uraemia due to acute tubular necrosis, but the safety margin is likely to be greater than that of conventional anti-tumour compounds.

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Photosynthesis and Gas Exchange of *Acetabularia* Chloroplasts in an Artificial Leaf

ISOLATED chloroplast preparations offer great advantages in the analysis of carbon pathways of photosynthesis because the system is not complicated by non-chloroplast metabolism, and kinetic analyses¹ can be made which are difficult with whole leaves². Unfortunately the slow diffusion and equilibration of CO_2 , HCO_3^- and CO_3^{2-} in the suspension medium is a serious disadvantage in gas exchange or $^{14}\text{CO}_2$ - $^{12}\text{CO}_2$ pulse-chase experiments³, but this difficulty can be overcome by using a thin film of concentrated chloroplast suspension spread on a non-absorbent support in the form of an "artificial leaf". Recent experiments by Coombs and Baldry have shown that pea and spinach chloroplast preparations supported on filter paper were stable only for periods of up to 10 min⁴. We have used *Acetabularia mediterranea* chloroplasts on filter paper to analyse the products of short term (1 s to 5 min) $^{14}\text{CO}_2$ fixation, but we found them insufficiently stable for longer experiments or gas exchange measurements. We have overcome this difficulty, however, by supporting chloroplasts on a non-absorbent grid instead of filter paper.

Acetabularia chloroplast preparations are made using mannitol isolating and suspending media³ at pH 7.6. An artificial leaf is made by spreading a preparation containing 2 mg of chlorophyll/ml. evenly on a double layer of 74 mesh nylon bolting cloth stretched on a plastic frame. This is placed in a leaf chamber at 25° C in a closed circulating gas system with an infrared CO_2 analyser for gas exchange measurements³. The air entering the chamber is saturated with water and dried by a condenser before entering the CO_2 analyser. The humidifier contains distilled water and carbonic anhydrase; no measurable CO_2 absorption, retention or release occurs in the system lacking only chloroplasts. The size of the artificial leaf can be varied to suit experimental needs. Most experiments were done with a leaf of 6.5 cm diameter made with 0.50 ml. chloroplast suspension (about 15 $\mu\text{l./cm}^2$).

Using this system photosynthesis begins immediately on illumination and reaches a maximum rate after a few seconds (Fig. 1). On darkening, CO_2 uptake stops abruptly and CO_2 evolution begins. Linear rates of CO_2 uptake or evolution can be maintained for at least 90 min. The CO_2 saturation curve for the artificial leaf is compared in Fig. 2 with that of chloroplasts in liquid system and intact cells in seawater. The three systems are quite similar, with CO_2 saturation occurring at approximately 0.18% CO_2 and compensation point at approximately 0.018% CO_2 . Both saturation and compensation points are considerably higher than those usually found

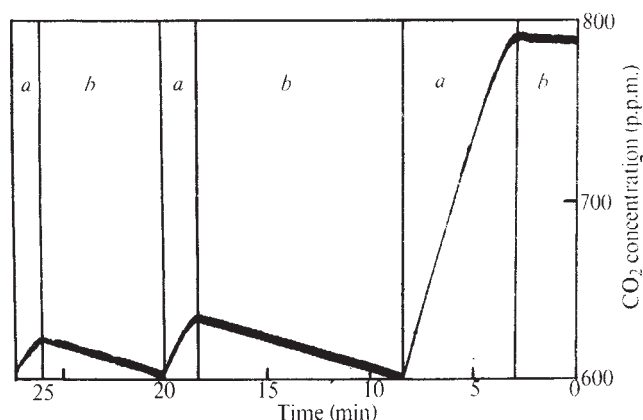


Fig. 1 A record of CO_2 exchange by an artificial leaf made with *Acetabularia* chloroplasts. O_2 content was 2%, light intensity 1,200 foot candles. The slopes correspond to rates of dark respiration of 5.1 μmol and photosynthesis of 72 μmol $\text{CO}_2/\text{h/mg}$ chlorophyll. a, Light; b, dark.

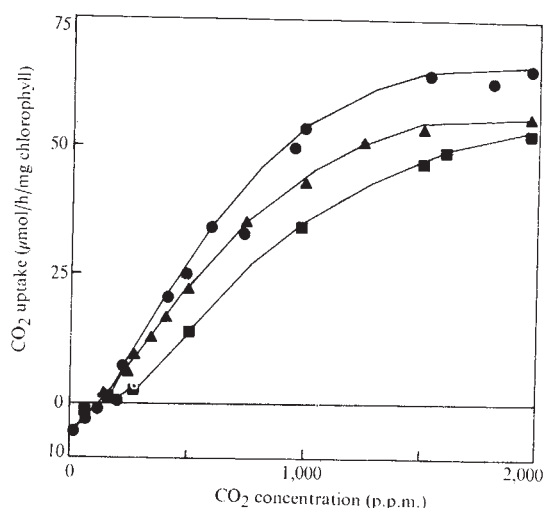


Fig. 2 The effect of CO_2 concentration on photosynthesis of chloroplasts in liquid medium (▲), of whole cells (■), and of the artificial leaf (●).

in leaves of higher plants. This presumably reflects the different CO_2 plus HCO_3^- concentration in the environment, the levels in seawater being several times higher than CO_2 in air. The effect of light intensity on photosynthesis is essentially similar in both the artificial leaf and in suspended chloroplasts (Fig. 3). Rates of CO_2 fixation by the artificial leaf up to two or three times higher than the rates in a liquid system have been observed using the same chloroplast preparation.

Table 1 Effect of O_2 Concentration on Dark Respiration, Photosynthesis and Photorespiration in an Artificial Leaf of *Acetabularia* Chloroplasts, as $\mu\text{mol CO}_2/\text{h/mg Chlorophyll}$

O_2 concentration	Dark respiration		Photosynthesis	Photorespiration in O CO_2
	after 30 min darkness	after 15 min illumination		
1.5	3.6	6.0	58	0
21	4.6	6.0	36	2.4
50	4.2	6.3	18	3.6

The effect of O_2 and CO_2 exchange in light and darkness is shown in Table 1. Photosynthesis is strongly inhibited and photorespiration is stimulated by O_2 , as in the leaves of higher plants⁵. Dark respiration is unaffected by oxygen in the concentration range used. The fact that dark respiration increases after a period of photosynthesis confirms that recent photosynthate is a substrate³.

The data of Coombs and Baldry⁴ indicate that the density of pea or spinach chloroplast suspensions influences the pattern of photosynthetic carbon incorporation into intermediates.

Table 2 Distribution of ^{14}C among Products of 10 min Photosynthesis in $^{14}\text{CO}_2$ by Chloroplasts in Liquid Suspension, the Artificial Leaf, and Whole Cells of *Acetabularia*, as a Percentage of Total ^{14}C Fixed

Compound	Chloroplasts	Artificial leaf	Whole cells
Insoluble	54.7	55.2	61.7
Sugar diphosphates	0.6	0.5	2.3
Hexose monophosphates	3.3	0.9	1.1
Phosphoglyceric acid	2.5	1.0	11.1
Triose phosphates	0.7	0.5	0.5
Sucrose	14.4	18.9	7.9
Glucose	—	—	2.5
Glycolic acid	4.6	1.8	0.9
Aspartic acid	4.4	5.0	2.0
Glutamic acid	0.6	0.9	0.4
Serine	2.9	4.2	1.4
Glycine	2.1	1.1	2.1
Alanine	6.5	6.7	3.5
Malic acid	0.6	3.3	trace
Unidentified	2.1	trace	2.7

We have examined the incorporation of ^{14}C into the products of photosynthesis of *Acetabularia* using the artificial leaf, chloroplasts in liquid suspension and intact cells (Table 2). The chlorophyll content of the liquid system was $20 \mu\text{g/ml}$ and of the artificial leaf was 2 mg/ml . In spite of the 100-fold difference in the ratio of chloroplasts to medium, there is very little difference in the pattern of distribution of ^{14}C in the products of photosynthesis of chloroplasts. The quantitative differences between the patterns for chloroplasts and whole cells are due in part to the difference between the pH of the suspending medium (7.5) and that of the cytoplasm (8.2–8.4)⁶.

Table 3 Gas Exchange and Products of Photosynthesis by *Acetabularia* Chloroplast Preparations in ^{14}C -Bicarbonate (pH 8)

Gas exchange	$\mu\text{mol CO}_2/\text{h/mg chlorophyll}$	
	Crude preparation	Purified preparation
CO_2 uptake in light	52	45
CO_2 production in dark	12	7
Products of photosynthesis ^{14}C -content, % of total fixed in 10 min		
Insoluble products	20.4	25.1
Sucrose	8.9	9.1
Triose phosphate	1.1	1.2
Hexose monophosphate	5.6	8.3
Sugar diphosphate	11.0	7.4
Phosphoglyceric acid	6.9	5.0
Glycolic acid	23.3	21.3
Glyceric acid	0.7	0.5
Malic acid	0.9	0.3
Citric acid	0.1	0
Succinic acid	0.1	0
Alanine	3.9	7.5
Serine + glycine	12.9	11.4
Aspartic acid	3.6	2.4
Glutamic acid	0.6	0.5

The crude preparation was centrifuged only once (500g, 5 min) after isolation, and contained many large droplets of cytoplasm, chloroplasts and mitochondria. The purified preparation was further homogenized and centrifuged, and contained only small droplets and a few mitochondria.

These data differ in several respects from those of Coombs and Baldry⁴. *Acetabularia* chloroplast preparations have unusual stability which may be due to the relatively impermeable outer membrane which prevents loss of photosynthate¹. The ability of these chloroplast preparations to synthesize sucrose, their high rate of photosynthesis without lag phase, and their dark respiration, may be due in part to the retention of important enzymes, co-factors or intermediates by this membrane. The level of cytoplasmic contamination is low in these preparations, but some mitochondria are present³. The amount of such contamination can be varied experi-

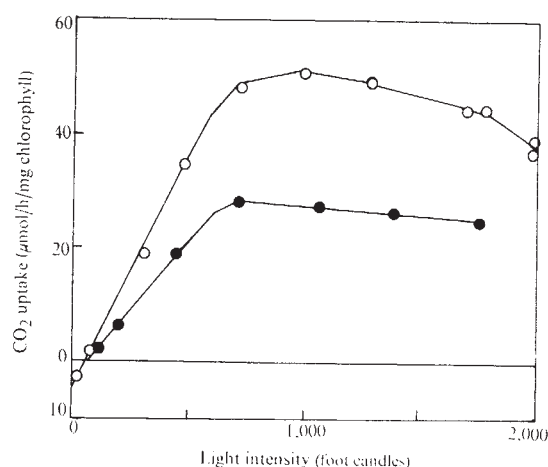


Fig. 3 The effect of light intensity on photosynthesis of chloroplasts in liquid medium (●) and the artificial leaf (○) at 500 p.p.m. CO_2 .

mentally, however, and does not affect the entry of ^{14}C into major products of photosynthesis (Table 3). We therefore conclude that much of the photosynthesis metabolism under study is that of chloroplasts and not of the small amount of contaminants present. Purification reduces the rate of CO_2 fixation slightly, but it reduces the rate of dark respiration rather more (Table 3). Therefore the dark respiration may be attributable to cytoplasmic impurities.

The artificial leaf using an *Acetabularia* chloroplast preparation is a stable system, capable of normal photosynthesis. Because of its experimental convenience, and the similarity of its behaviour with that of chloroplast suspension and whole cells, it is potentially valuable for studying the intermediary metabolism and control mechanisms of photosynthesis and photorespiration.

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Transfer of Nitrogen-fixation Genes by Conjugation in *Klebsiella pneumoniae*

THE study of biological nitrogen fixation at the genetic level has been restricted by the lack of a suitable method of gene transfer in nitrogen-fixing bacteria. Mutants of *Azotobacter vinelandii*^{1,2} and *Clostridium pasteurianum*³ defective in nitrogen fixation have been isolated and characterized, but the transfer and mapping of the nitrogen fixation (*nif*) genes have not so far been possible.

The species *Klebsiella pneumoniae* includes strains which fix nitrogen if the environment is anaerobic. Matsumoto and Tazaki⁴ have described fertile strains of *K. pneumoniae* which bring about gene transfer by conjugation and they have constructed a genetic linkage map of *K. pneumoniae*⁵ which is similar to that of *Escherichia coli* and *Salmonella typhimurium*. We have found that these fertile *K. pneumoniae* strains do not fix nitrogen. Some of the transmissible bacterial plasmids which promote genetic recombination in other genera of the Enterobacteriaceae, however, are readily transferred to *Klebsiella* strains. Here we report the occurrence of chromosome transfer, mediated by a de-repressed R factor, in the nitrogen-fixing strain *K. pneumoniae* M5a1. We also report the transfer by conjugation of nitrogen-fixation genes from wild type *K. pneumoniae* to mutants defective in nitrogen fixation (*nif*⁻) and present preliminary linkage data on some nitrogen fixation markers.

The strain used, *Klebsiella pneumoniae* M5a1, is a nitrogen-fixing organism originally isolated from a 2,3-butanediol

fermentation⁶. It gave no transfer of chromosomal markers in matings with auxotrophic derivatives of *K. pneumoniae*, strain K1-8, provided by Dr H. Matsumoto, which is known to act as a recipient of genetic material⁴. However, chromosomal transfer was brought about in M5a1 by introducing a de-repressed I-type R factor, R144drd3, into this strain from its original host, *E. coli* J53. R144drd3 transferred chromosomal genes to auxotrophic M5a1 recipients at slightly lower recombination frequencies than those reported for this sex factor in F⁻ *E. coli* K12 (ref. 7) (Table 1). However, when M5a1 was mated with *E. coli* carrying the F-like R factor mutants R1drd19 to R1drd16, M5a1 clones were obtained which were characteristically drug-resistant, but which gave no transfer of drug resistance markers in matings with F⁻ *E. coli* K12 and were resistant to F-specific phage. In contrast, M5a1 carrying R144drd3 transferred drug resistance at high frequency to K12 and was sensitive to I-specific phage. It therefore seems likely that the drug resistance determinants of these two de-repressed F-like R factor mutants became segregated from the sex factor during transfer to M5a1. A similar phenomenon has been observed with R factor transfer in *Salmonella typhimurium*⁸.

Table 1 Characteristics of *K. pneumoniae* M5a1 after Mating with *E. coli* Strains carrying De-repressed Mutant R Factors

De-repressed R factor	Drug resistances conferred	Chromosomal recombinants per donor cell for	Sensitivity to male specific phage
		<i>leu</i> ⁺ <i>his</i> ⁺	μ_2 if ₂
None	—	<10 ⁻⁹ <10 ⁻⁹	— —
R144drd3	Km	2 × 10 ⁻⁵ 4 × 10 ⁻⁵	— +
R1drd16	Km Cm Ap Sm Su	<10 ⁻⁹ <10 ⁻⁹	— —
R1drd19	Km Cm Ap Sm Su	<10 ⁻⁹ <10 ⁻⁹	— —

E. coli strains carrying the de-repressed mutant R factors were mated with *K. pneumoniae* M5a1, drug-resistant recipient M5a1 clones were purified and mated with auxotrophic streptomycin-resistant derivatives of M5a1. One volume of donor culture grown to log phase in broth (2 to 5 × 10⁸ organisms/ml.) was added to 9 volumes of recipient culture and incubated for 4 h at 37° C without shaking. The bacteria were then centrifuged, resuspended in buffer and plated at various dilutions on selective media to determine the number of recombinants and the number of donor cells present. Streptomycin was used to counter-select the donor at 250 µg/ml., or 2 mg/ml. where the R factor carried a determinant for streptomycin resistance. Phage sensitivities were measured by spotting phage on to semi-solid nutrient agar overlays containing the bacteria under test. + Indicates visible lysis.

To study the transfer of nitrogen fixation markers, a series of mutants of *K. pneumoniae* M5a1, defective in nitrogen fixation (*nif*⁻), were isolated as follows. A streptomycin-resistant derivative of M5a1 was mutagenized with 20 mM isopropylmethane sulphonate for 1 h at 37° C, washed by centrifugation to remove the mutagen and then grown in air overnight in nutrient broth to allow segregation of mutant phenotypes. The mutated culture was then washed by centrifugation to remove fixed nitrogen and was sparged with N₂ for 18 h at 34° C to allow induction or de-repression of nitrogenase. Penicillin (16,000 IU/ml.) and D-cycloserine (1 mg/ml.) were then added and the culture was sparged with N₂ for a further 6 h to enrich *nif*⁻ mutants. Surviving bacteria were collected on a membrane filter and washed free of the antibiotics before further growth in nutrient broth. After several such antibiotic enrichments, *nif*⁻ mutants were sought by plating anaerobically under N₂ on minimal medium containing low nitrogen as 10 µg NH₄Cl-N/ml. Presumptive *nif*⁻ mutants were small and colourless on this medium whereas the wild type produced large colonies which were distinctly yellow. The acetylene-reducing activity of the presumptive *nif*⁻ isolates was almost negligible compared with wild type (Table 2), indicating that these mutants are defective in nitrogen fixation. Full details of the biochemical properties of these mutants will be published later.

Table 2 Comparison of Acetylene Reduction in Wild Type, *nif*⁻ Mutants and *nif*⁺ Recombinants of *K. pneumoniae* M5a1

Strain	nmol ethylene formed/min/mg dry weight
Wild type	20.7
<i>nif</i> 12	0.3
<i>nif</i> 2	<0.1
<i>nif</i> 3	<0.1
<i>nif</i> 9	<0.1
<i>nif</i> ⁺ 3 recombinant	18.1
<i>nif</i> ⁺ 9 recombinant	17.4

The bacteria were grown in a modified Hino and Wilson's N-free medium¹⁰ supplemented with 1 mg of yeast extract/ml. in "medical flat" flasks sparged with N₂ at 30° C. Samples of 2 ml. were removed from the culture and tested for acetylene reduction under argon at 30° C in sealed 25 ml. flasks containing 1 ml. of acetylene which were shaken slowly.

Crosses were performed between *K. pneumoniae* M5a1 carrying R144drd3 and *nif*⁻ mutants of M5a1. *Nif*⁺ recombinants were selected for anaerobically on nitrogen-free minimal medium. The donor was counter-selected with streptomycin; the concentration, 5 mg/ml., was high because this antibiotic is far less effective in anaerobic conditions. In typical crosses, nitrogen-fixing recombinant colonies appeared at a frequency of approximately 10⁻⁵ per donor organism. Recombinant colonies after purification on nitrogen-free minimal medium gave acetylene-reducing activity equivalent to the wild type (Table 2).

We have also transferred an unidentified sex factor, from Matsumoto's *Klebsiella* strain D8, to M5a1 and obtained a fertile M5a1 strain which transferred genetic information, including *nif*, to M5a1 recipients. The recombination frequencies, however, were very low and the system was not studied further.

While this work was in progress, Streicher, Gurney and Valentine⁹ reported the transduction of the nitrogen fixation genes in *K. pneumoniae* M5a1 using bacteriophage P1 and showed that several *nif* genes were located near the histidine operon on the linkage map of *K. pneumoniae*; we acknowledge advance information on their findings from Dr R. Valentine. Their observations prompted us to consider the relationship of the *his* and *nif* loci. Crosses were performed between M5a1 (R144drd3) and multiple auxotrophic *nif*⁻ mutants of M5a1, the recombinants were purified on selective media and then scored for inheritance of *nif*. We find that *his* shows a 95% linkage to *nif* 9 and an 85% linkage to *nif* 2, thus confirming that *his* and *nif* are closely linked.

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Metabolism of Δ^9 -Tetrahydrocannabinol by Lung and Liver Homogenates of Rats treated with Methylcholanthrene

Δ^9 -TETRAHYDROCANNABINOL (Δ^9 -THC) is metabolized *in vitro* by the postmitochondrial supernatant of rabbit liver to yield 11-hydro- Δ^9 -THC¹, said to be as pharmacologically active as Δ^9 -THC itself^{2,3}, while at least two other metabolites have been detected². Because psychoactive cannabinoids are effective in cannabis smoking, we have studied the transformation of Δ^9 -THC by the postmitochondrial supernatant of the rat lung and we have compared the chromatographic properties of the Δ^9 -THC metabolites which were produced *in vitro* by the postmitochondrial supernatant of liver and lung from untreated rats and from rats pretreated with 3-methylcholanthrene⁴.

Young male Sprague-Dawley rats (Zivic Miller, Pittsburgh, 50–60 g) were injected intraperitoneally with 3-methylcholanthrene (20 mg/kg) in 0.25 ml. of sesame oil daily for 4 days. Control rats were given injections of sesame oil. Each group consisted of three rats, fed liberally with Purina chow. The rats were decapitated, the livers were quickly removed, chilled in an ice bath and homogenized with five volumes of 0.25 M sucrose, while the lungs were homogenized with ten volumes of the same sucrose solution. The homogenates were centrifuged at 9,000g for 20 min at 0°–5° C and the subsequent postmitochondrial supernatant was used as the enzyme source. The reaction mixture contained, in a total volume of 0.50 ml., 17.7 nmol Δ^9 -THC-¹⁴C (12,500 d.p.m./nmol), 1 μ mol glucose 6-phosphate, 100 nmol NADP, 100 nmol nicotinamide, 1 μ mol MgCl₂, 1 U glucose 6-phosphate dehydrogenase, 30 μ mol Tris-HCl (pH 7.4) and 0.03 ml. (0.45 mg protein) of the postmitochondrial supernatant in the case of liver, or 0.20 ml. (1 mg protein) in the case of lung. (Δ^9 -THC-¹⁴C, which was synthesized by Research Triangle Institute, North Carolina, is labelled on the 2- and 4-positions of the benzene ring; its specific activity is 5.5 mCi/nmol.) The mixture was incubated for 15 min at 37° C and the reaction was stopped by shaking vigorously with 10 ml. of petroleum ether and 2.0 ml. of distilled water for 5 min in a separating funnel. The cannabinoids in the aqueous phase were then removed with ethylacetate. These two organic phases extract the radioactivity almost completely. After evaporation to dryness the radioactive compounds were dissolved with a small amount of dehydrated ethanol and applied on thin-layer plates with silica gel G. Δ^9 -THC and its metabolites were chromatographed twice, with a solvent system of cyclohexane-diethyl ether (4:1) followed by another solvent system of chloroform-cyclohexane-acetic acid (50:40:10). The spots of nonradioactive compounds were detected by spraying the plate with 0.2% O-dianisidine tetrazolium chloride (fast blue salt B) in 2 M NaOH⁵; the radioactive spots could be detected by autoradiography. The radioactivity of the absorbent scraped from the plates was determined by liquid scintillation counting. Protein was determined by the method of Lowry *et al.*⁶.

Δ^9 -THC-¹⁴C was incubated with the postmitochondrial supernatant of lung and liver in the conditions described. When an aliquot of the reaction was extracted and chromatographed on the thin-layer plate, several radioactive products as well as Δ^9 -THC-¹⁴C could be detected (Fig. 1). Co-chromatography with authentic samples of Δ^9 -THC, Δ^8 -THC and 11-hydroxy- Δ^8 -THC corroborated that Δ^8 -THC could not be distinguished from Δ^9 -THC by this method and that the *R_F* of 11-hydroxy- Δ^8 -THC was 0.30. This result suggests that the radioactive metabolite with an *R_F* of 0.30 may be 11-hydroxy- Δ^9 -THC.

We compared the enzymatic production of several radioactive metabolites from Δ^9 -THC, by lung and liver of untreated rats and rats receiving 3-methylcholanthrene. The results are summarized in Table 1. The enzymes of the postmitochondrial supernatant of rat lung could produce several metabolites of

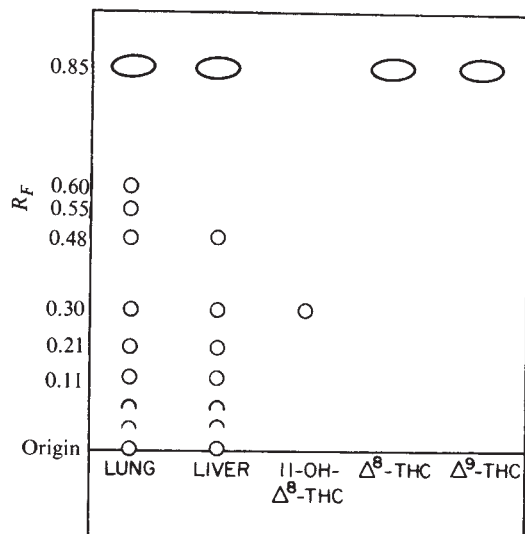


Fig. 1 Separation of Δ^9 -THC and its metabolites by thin-layer chromatography.

Δ^9 -THC. Moreover, by the pretreatment with 3-methylcholanthrene the metabolism of Δ^9 -THC was stimulated in the lung but not in the liver. In the liver, however, the enzyme activity responsible for the formation of compounds with R_F values of 0.30 and 0.48 was induced by 3-methylcholanthrene.

The compounds of R_F 0.60 and 0.55 were produced by the postmitochondrial supernatant of the lung, but they could not be detected when Δ^9 -THC was incubated with the liver homogenates. The compounds of R_F 0.48 were formed to a greater extent by lung supernatant than by liver supernatant. On the other hand, the enzymatic formations of the compounds with R_F 0.30 and 0.21 were more conspicuous in the liver than in the lung.

Generally, the liver is considered to be the principal site for the transformation of several drugs, but nonhepatic tissues such as the lung and the kidney can metabolize various drugs^{4,7-10}; on the basis of histochemical findings, for example, Wattenberg *et al.*¹⁰ reported that the alveolar walls of rat lung might be the metabolic site for 3,4-benzpyrene production. Our results show that Δ^9 -THC is also enzymatically converted by rat lung, but that the pathways of Δ^9 -THC metabolism in lung homogenates might be different from those detected in liver.

Ho *et al.*¹¹ administered Δ^9 -THC-³H by smoking and found that cannabinoids are retained by lung and that in this tissue, the radioactivity remains higher than in all other tissues for longer than 24 h. Moreover, the level of radioactivity in brain and liver is lower than that of lung for up to 7 days. This observation suggests that when Δ^9 -THC is administered by

smoking, the lung may be more important than the liver for the storage and biotransformation of Δ^9 -THC. We found that treatment with 3-methylcholanthrene induced the enzyme system responsible for the metabolism of Δ^9 -THC in the lung but had no effect on that in the liver. In the lung of rats receiving 3-methylcholanthrene the rate of Δ^9 -THC metabolism is equal to that in liver, suggesting that in these animals the lung plays a critical role in the biotransformation of Δ^9 -THC. We also found that liver homogenates of rats receiving phenobarbital (75 mg/kg) for 4 days metabolized Δ^9 -THC at a rate twice that of liver homogenates from untreated rats. The induction of lung but not of liver enzymes for Δ^9 -THC metabolism by polycyclic hydrocarbons may be consistent with a suggestion made by Mannering *et al.*¹² that a microsomal haemoprotein different from the so called P-450 is formed in the liver when 3-methylcholanthrene is administered. Possibly the enzyme system responsible for the metabolism of Δ^9 -THC in the lung recognizes a microsomal haemoprotein different from P-450, and this property may explain the selective induction of Δ^9 -THC metabolism by 3-methylcholanthrene in the lung. The precise mechanism of this selective induction by polycyclic hydrocarbons and the pharmacological implications of the different biotransformation of Δ^9 -THC in lung and liver is under investigation in our laboratory.

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Table 1 Effect of Methylcholanthrene on the Metabolism of Δ^9 -THC in Rat Lung and Liver

Metabolite	Radioactive metabolites formed (pmol/min/mg protein) $\pm$ s.d.			
	Lung		Liver	
	Control	3-MC *	Control	3-MC *
R_F 0.60	30.4 $\pm$ 4.1	42.4 $\pm$ 2.3	0	0
R_F 0.55	29.6 $\pm$ 1.2	45.4 $\pm$ 4.0	0	0
R_F 0.48	23.8 $\pm$ 2.5	78.1 $\pm$ 2.4	9.8 $\pm$ 2.9	27.3 $\pm$ 2.6
R_F 0.30 †	9.4 $\pm$ 5.0	15.6 $\pm$ 10.3	32.1 $\pm$ 15.5	94.6 $\pm$ 23.6
R_F 0.21	12.0 $\pm$ 3.1	19.8 $\pm$ 4.5	206.3 $\pm$ 53.0	120.1 $\pm$ 39.6
R_F 0.11	7.0 $\pm$ 5.0	19.1 $\pm$ 7.4	20.4 $\pm$ 5.5	33.0 $\pm$ 3.5
Total rate ‡ of Δ^9 -THC metabolism	172.8 $\pm$ 18.1	406.2 $\pm$ 36.8	358.5 $\pm$ 77.7	384.8 $\pm$ 102.7

* Injected intraperitoneally with 20 mg/kg of 3-methylcholanthrene.

† This compound may be 11-hydroxy- Δ^9 -THC.

‡ This value indicates the amount of metabolized Δ^9 -THC.

Fluid Friction of Fish Slimes

WHEN dissolved in water, the natural slimes of most of the fishes we have tested have a remarkable capacity to decrease greatly the friction of water when flowing in the turbulent state. In one species, a dilute solution of its slime was found to reduce the friction of water by as much as 65.9%; reductions of 57% to 63% were frequently obtained with the slimes of other species. These measurements have led us to the view that the slimes of many (but not all) fishes assist in locomotion by reducing the drag or resistance which water offers to their bodies.

Slime samples were taken from the live fishes immediately after removal from the water and after excess water had been drained off their bodies. The slime was diluted to various

concentrations with clean water from the natural environment and then tested in a portable rheometer.

The rheometer works on a principle described by Hoyt². A glass plunger (Fig. 1) drives the solution upwards through a stainless steel tube 6 inches long and 0.023 inch internal diameter. At two points, 3 inches apart, the tube is pierced with a side outlet, and the static pressure of the moving fluid at these two locations is sensed by electrical transducers and read directly on two meters. The rheometer was first calibrated using plain water.

In most cases, the pressure decrease measured with fish slime solution was substantially lower than that measured with plain water, and the corresponding reduction of friction can be calculated from the ratio of the two differences of pressure. The fluid velocity reached 45 feet per second, corresponding to a pipe Reynolds number of nearly 8,000, which in turn implies that the flow in the tube is well within the turbulent regime for water.

The results are shown in Fig. 2 for saltwater species and in Fig. 3 for freshwater species; and the slime of the Pacific barracuda, *Sphyrna argentea*, is the most effective reducer of friction of all the fish tested, with a maximum reduction of 65.9% when the natural slime is at 5% concentration. With more concentrated solutions, the friction reduction diminished slightly. The barracuda curve represents data taken from eleven individual fish all of the same species, 26–31 inches long, and caught on different days. The barracuda curve rises steeply for very low slime concentrations. A 44% friction reduction was obtained with a solution of only 3/4 of 1% barracuda slime (Fig. 4).

The results of the work with the slimes of halibut, *Paralichthys californicus*, and other sea species are also shown in Fig. 2. Halibut slime is almost as good a friction reducer as that of barracuda. The curves for most of the other species of saltwater and freshwater fishes shown are similar but do not rise as steeply as those of halibut and barracuda.

The measurements on California bonito, *Sarda chiliensis*, were a surprising exception. This slime seems to be almost ineffective as a reducer of water friction. Tests on specimens caught on different days gave consistent data, verifying ineffectiveness of this slime. Two sea animals that are not fishes have been included for comparison; the mollusc known as the nut brown cowry, *Cypraea (Zonaria) spadicea*, and the California hagfish whose slime was measured by J. Hoyt and W. White (personal communication). The maximum friction reduction obtained for each species is given as well as values of friction for low concentration solutions. The latter is important, for a slime which gives a large friction reduction at relatively low concentration in water is considered very effective. If slime is added to still water, it typically stays separate from it; we have called this property "reluctance". Most of the slimes, though not all, dissolve in water when stirred or agitated.

On the whole, the slimes of fishes seem to possess frictional properties which are adapted to the need of the species for speed, or to its life habits and activities. The barracuda, which had the most effective slime tested, is a streamlined predator (Fig. 4). The closely related species, *Sphyrna*

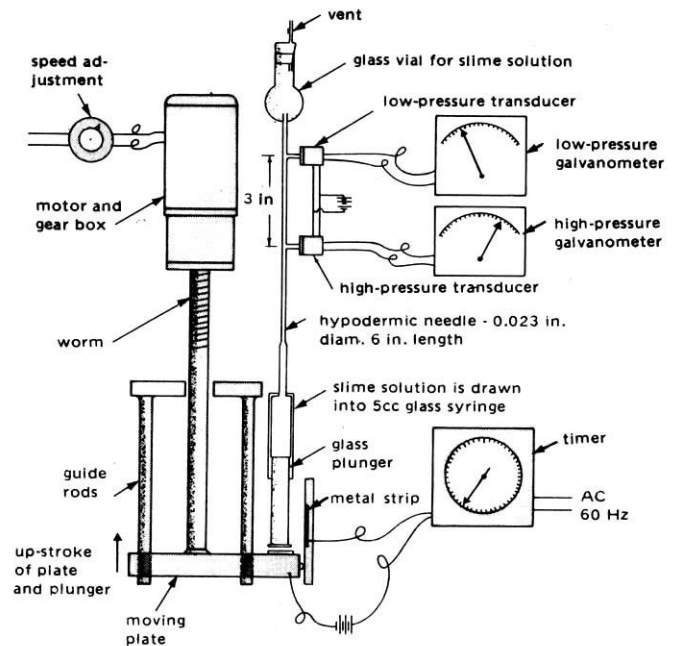


Fig. 1 Schematic diagram of rheometer.

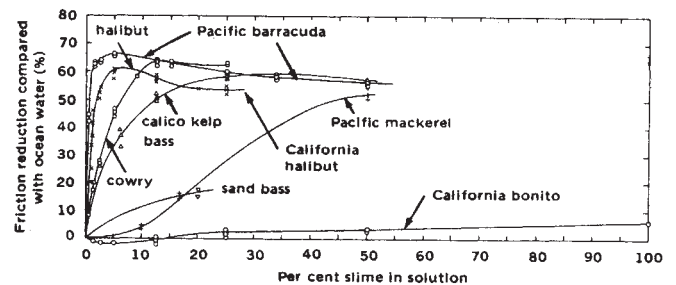


Fig. 2 Friction reduction of slimes of seawater fish when dissolved in ocean water in various concentrations.

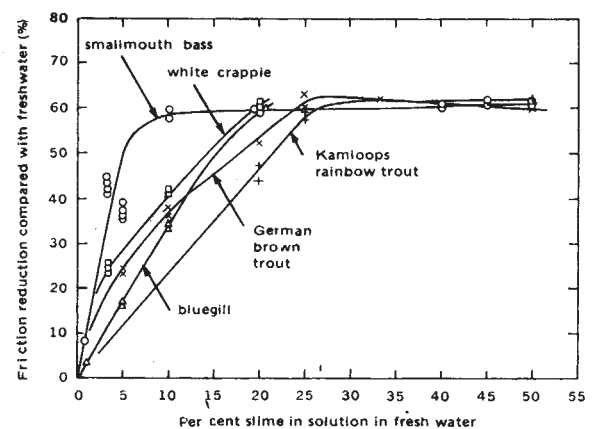
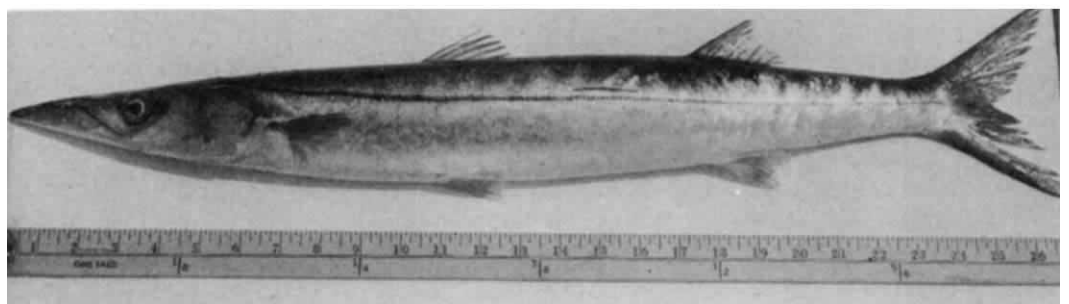


Fig. 3 Friction reduction of slimes of freshwater fish when dissolved in fresh water in various concentrations.

Fig. 4 Pacific barracuda.



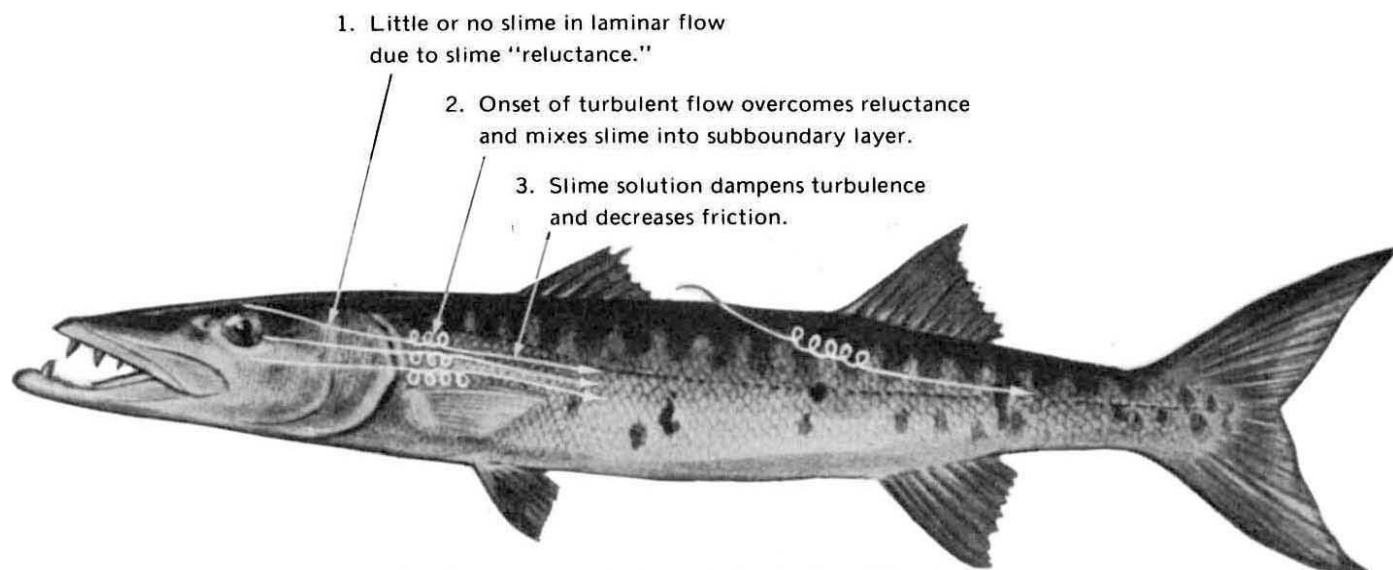


Fig. 5 Rosen-Cornford hypothesis of action of fish slime.

barracuda, has been measured by D. Gero³ to swim at 27.3 miles/h, which is very fast for an aquatic animal. The halibut, which also has effective slime, catches fish by means of long, swift lunges.

The trouts are reasonably swift swimmers, and the slimes of the adults are correspondingly fairly effective. On the other hand, the California hagfish has no need for speed, being a parasite and scavenger. Its slime, although thick and profuse, is a poor reducer of water friction. The slime of this animal could not be dissolved except by forcibly homogenizing it with water in a mechanical blender. Similarly, the white croaker, which feeds on slow sea life and has little need for speed, has a thick curdy slime, insoluble in seawater, and which could not be put through the rheometer. Two exceptions are the slimes of the Pacific mackerel, *Scomber japonicus*, and the California bonito, both of which are fast swimmers. The mackerel's slime becomes effective only at a concentration of 50% slime, 50% water; and that of the bonito produces no more than 6.4% friction reduction at 100% concentration. Perhaps this fish attains its propulsive speed in other ways, possibly by the formation of a large organized vortex system at its sides, similar to the remarkable fish vortex system discovered by Rosen⁴. The slime of the nut brown cowry was quite effective as a friction reducer. Although this animal has no need for speed, its slime provides good lubrication between its tissues and its hard shell as it moves about.

The amount of solid substance in the slime of the small mouth bass, *Micropterus dolomieu*, was measured by weighing the residue left after the water had evaporated under a vacuum at room temperature. We found that the natural slime as taken from the fish consists of only 0.153% solids by weight, and possibly half of this is water of crystallization. With an assumption that barracuda slime would contain about the same percentage of solids, and taking the measurement that a 1.5% barracuda slime solution produced a friction reduction of 62.9%, we compute:

$$\frac{0.153}{100} \times 0.5 \times \frac{1.5}{100} = 0.0000115$$

This means that the barracuda may need to supply only about 11.5 parts of its own organic solid substances to every million parts of water flowing in the boundary layer over its body in order to decrease water friction by 62.9%. Similarly, this fish, with a 3/4 of 1% solution, need supply only 5.7 p.p.m. of its organic solid substances to decrease water friction by 44%.

We propose the following hypothesis (Fig. 5). Most of the time, fishes swim quite slowly and the sub-layers of water very close to the body may not be turbulent. The "reluctance"

of the slime prevents the loss of the slime coat. But during the short periods when the fish must swim rapidly to catch its prey, or to escape danger, the sub-layers of water break into turbulent flow and the reluctance of the slime is overcome, so that a small amount goes into solution. The turbulence at that point automatically produces its own suppression, for the dilute slime solution it has created dampens further turbulence and flows with lower friction over the scales. As the fish swims more rapidly its body is enveloped by a thin boundary layer of this extremely dilute slime solution which suppresses any turbulence and substantially lowers the water friction on the body. Thus with only a minute expenditure of organic solid substances to make the necessary quantity of slime solution, the fish can attain a considerably higher speed than would otherwise be possible.

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Anoxia in Mosquito Pupae under Insoluble Monolayers

THE dependence of mosquito larvae and pupae on the air-water interface for respiration suggests several opportunities for insect control. The use of soluble surfactants to vary the surface tension¹⁻³ is reported to have been effective but the substances employed would not be used on water intended for drinking or irrigation. Insoluble monomolecular layers of lauryl alcohol have also been reported⁴ to be effective against pupae of *C. pipiens quinquefasciatus*. We now describe the effect of several monomolecular films on mosquito pupae of several species.

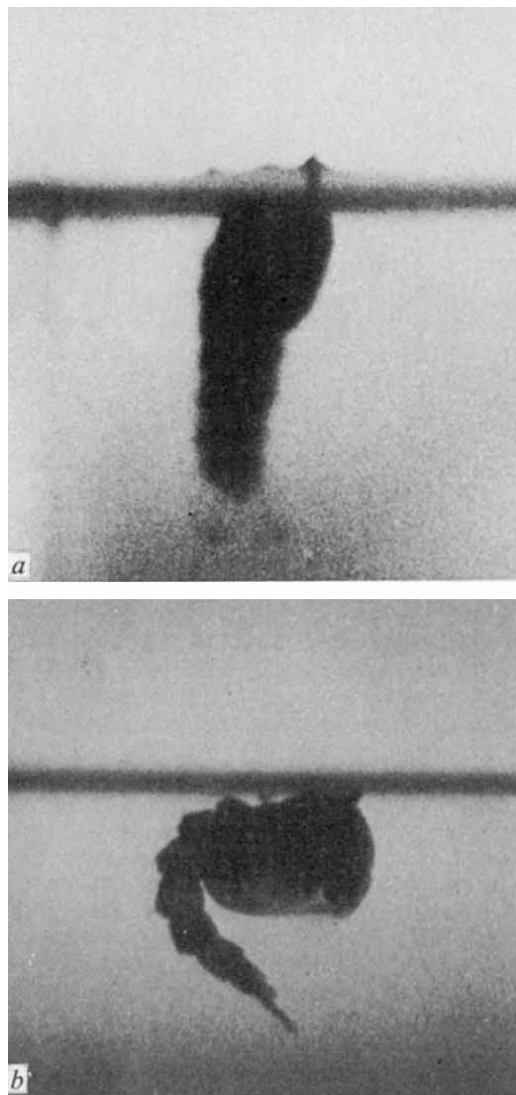


Fig. 1 *a*, An energetic but unsuccessful attempt by a mosquito pupa to penetrate a monolayer of lipid (from a high speed cine sequence taken at 240 frames/s). *b*, Mosquito pupa in the normal respiring position.

The study described here began with the observation that a monolayer of crude lipid extract was 100% lethal to pupae of *Anopheles (Cellia) stephensi* Liston, and to pupae of *Aedes (Stegomyia) aegypti* (Linnaeus) in the underlying water. The method has since proved equally successful with all other species investigated, for example, *An. albimanus*, *An. atroparvus*, *An. gambiae*, *An. quadrimaculatus*, *An. phaeoensis* and *Culex fatigans*. For comparison, the effect of other insoluble monolayers having a range of maximum equilibrium spreading pressures (π_e) was determined at a constant temperature of 27° C. Surface pressures were measured by the pull on a thin glass slide supported in the interface by a sensitive electro-balance. The vessel, containing about forty pupae in distilled water, was temperature equilibrated; the water surface was cleaned to constant tension by suction and this reading on the balance was taken as zero pressure. The film was spread and the maximum pressure noted. The number of successful adult emergences, the number of adults trapped by surface tension forces at the interface, and the number of pupal deaths were recorded. Table 1 presents the results obtained using *Ae. aegypti*.

The results clearly indicate a critical pressure of approximately 45 dynes/cm, beyond which 100% mortality occurs in the pupal stage. Below this surface pressure a percentage of the emergent adults fails to get off the surface and dies. The total

mortality therefore remains high even if the film is incompletely spread and consequently not exerting its full pressure. The mechanism responsible for adult mortality is seemingly a "wetting process" which causes submergence of the legs and a general loss of flotation. This is observed readily by viewing the undersurface of the film. Evidence from high speed cine photographs⁵ indicated that the lipid monolayer was behaving more like an elastic membrane at full pressure, thus preventing any penetration by the respiratory trumpet of the pupa. Pupae at the film surface exhibit characteristic patterns of movement which include energetic attempts to force one pupal trumpet through the film by sideways-orientated circular movements and frequent efforts apparently to dislodge the film with the tail (Fig. 1*a*). Death occurs after 2–3 h, but before this the pupae sink to the bottom of the container and are unable to reach the surface; they exhibit violent flexing movements of the body and tail, probably due to a build up of lactic acid and other anaerobic metabolites in the muscles. Identical behaviour and a similar pattern of death were observed when a glass plate was placed on a normal water surface to exclude all air.

Table 1 Effect of a Range of Insoluble Monolayers on Mortality of *Aedes aegypti* Adults and Pupae

Film substance	π_e dynes/cm	Percentage of total kill as:	
		Adults	Pupae
None	0	0	0
Lysophosphatidyl ethanolamine	24.9	0	0
Methyl palmitate	28.0	0	0
Oleic acid	32.0	0	0
Cetyl alcohol	34.6	0	0
Cholesterol	38.0	35.0	0
Phosphatidyl serine	41.4	32.5	0
Lauryl alcohol	43.2	40.0	0
Dog brain lipid	45.7	0	100
Egg lipid	47.9	0	100
Egg lecithin	49.0	0	100
Glass plate	—	0	100

Attempts to asphyxiate larvae by the same methods were relatively unsuccessful, probably because of the different structure of the small larval spiracle which easily penetrated films of even the highest surface pressure. Other workers, however, have reported⁴ that larvae are killed under lauryl alcohol films.

Bio-degradable, non-toxic (edible) lipids, spread at the surface saturation concentration of about half an ounce per acre of water, afford a potentially valuable method of mosquito control. Such films are insoluble in water, do not prevent gaseous exchange across the air–water interface and are therefore in no sense destructive of aquatic (fish or plant) life. Because the films are a physical rather than a chemical "block" to pupal development it seems less likely that genetically resistant strains will arise. Effective methods of application in the field (particularly on ricefields and in water storage containers), including automated procedures, are to be investigated.

We thank D. Sainsbury for assistance with the surface pressure measurements, the CDE Film Unit for preparation of the movie sequences, and J. G. Broadfoot for larvae and pupae.

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BOOK REVIEWS

Threats to the Reef

The Struggle for the Great Barrier Reef. By Patricia Clare. Pp. 224+15 plates. (Collins: London and Sydney, September 1971.) £2.50.

THE Great Barrier Reef of Australia is a vast complex of coral reefs which extend in length for more than 1,200 miles and occupy widths ranging from 16 to 200 miles off the coast of Queensland. Nobody who has spent more than a year upon it over 40 years ago, as I did, could have dreamt of its ever being endangered or that the question of its conservation could emerge as a major political issue.

But this is certainly what has happened and the sequence of events leading to this is well presented in this book by Patricia Clare. Disregarding a few purple patches, the reader will find a very clearly written story. Although there is no doubt where the author's sympathies lie, she has visited and interviewed widely and judiciously and presents both sides of the argument. This book is first-rate journalism; too good, incidentally, not to have an index.

Relevant additional reading for readers who are particularly interested in the subject, and which is not specifically mentioned in this book, are two articles by Dr D. W. Connell, president of the Queensland Littoral Society (*Biological Conservation*, 3, 60; 1970; and 249; 1971), and a booklet, *The Future of the Great Barrier Reef*, which consists of a series of contributions presented at a symposium conducted by the Australian Conservation Foundation in the University of Sydney in May 1969.

Dangers facing the reefs are manifold—industrial and agricultural pollution, tourism, mining for coral rock and, most sinister, now also oil prospecting. Tourism is an insidious influence; a gradual spread of often tasteless and wasteful exploitation which largely affects inner and southern reefs but now reaches out to a most northern and off-shore base at Lizard Island, a high rocky island within sight of the outermost ribbon reefs and only a little south of Cook's Passage.

Such invasion, which equally affects remote Pacific islands, is unlikely to be stopped, but at least some moderation should be imposed on the indiscriminate collecting of shells and corals, of sport fishing and of underwater spear fishing. These spectacular invertebrates and fishes are often hunted to near extinction. One theory as to the cause of the plague of crown-of-thorns starfish which are destroying reef corals over widely scattered areas in the Pacific attributes

it to the collection of the large trumpet shell, *Charonia tritonis*, which preys on these starfish. But the more universal effect of pollutants, notably pesticides, has also been introduced as the chief cause of an underlying ecological imbalance.

Certainly the population explosion of this starfish first drew public attention to dangers affecting the Barrier Reefs, but confrontation came in 1967 when conservation interests, stimulated, as Patricia Clare describes, by action of the devoted few, proved great enough, when backed with soundly based argument, to ensure the rejection in the mining warden's court of an application to mine Ellison Reef for limestone. And this decision was made in spite of the urgent need for lime on the sugar cane fields of North Queensland. The effects of bauxite processing and of open cast mining for coal around Gladstone nevertheless become increasingly apparent.

With the later prospect of oil drilling, both State and Commonwealth Governments come into the picture. A report by Dr Harry Ladd, a most distinguished American reef geologist, approved exploitation under appropriate controls. Early last year, with the scene set for the operation of the oil-rig Navigator, the trade unions took action by threatening a ban on all goods and services. Clash of opinion between State and Commonwealth was resolved by the then Prime Minister, Mr Gorton, who stated that "In my view the slightest danger is too much danger" (a sentence that will surely endear him to all conservationists) and a Royal Commission, now sitting in Brisbane, was set up. The commission is unlikely to report before late in 1972.

This action by the Australian Government can be regarded as a triumph for conservation. Time is probably on that side but the real danger is lack of precise biological knowledge about coral reefs. What some of us began on the Barrier in 1928–29 has, for lack of public interest and money, had little addition. Only the Japanese, at their biological station at Koror in the Palau Isles, took biological studies somewhat further but their laboratory was destroyed in the war. There are now prospects of a Marine Research Institute to be built by the Commonwealth Government at Townsville in close proximity to the vigorous new James Cook University of North Queensland.

There is likelihood too of greater co-ordination of wider coral reef studies under the auspices of the Pacific Science Association. But knowledge in this

field is painfully slow in coming. All interested in conservation generally and in coral reefs in particular must applaud those few Australians whose efforts, so well related in this book, have stimulated the growth of public concern in the conservation of the Great Barrier Reef and so in the study of its richly varied ecosystems.

C. M. YONGE

Thermogenesis

Nonshivering Thermogenesis. (Proceedings of the Symposium held in Prague, April 1–2, 1970.) Edited by L. Jansky. Pp. 310. (Academia: Prague, 1971.) (Distributed by Butterworths, London.)

THERE is much justification for the popular and cynical view on symposium proceedings that if the contributions are worthy of note they either have been or will be published elsewhere. Thus library and laboratory shelves are cluttered with the neglected literary remnants of scientific symposia. However, it would be a great pity if this particular series of review and research papers by a small group of internationally acknowledged leaders in the field of thermoregulatory thermogenesis were to suffer such treatment.

That heat production in response to cold stress may not always involve the contractile activity of muscles was first proposed by Claude Bernard in 1876, but convincing demonstrations of the phenomenon were reported only ten to twenty years ago. The subsequent quest for the sites and the nature of nonshivering thermogenesis was enlivened, but certainly not resolved, by R. Em. Smith's discovery in 1960 of a special role of brown adipose tissue in the nonshivering thermogenesis of the white rat. Only those researchers directly and intimately involved in the study of cold-induced thermogenesis can be thoroughly conversant with the now vast literature pertaining to this complex and controversial subject. For those of us who are outside this immediate field it has become increasingly difficult to maintain a balanced appraisal of the accumulating evidence. It involves the contribution of different tissues in nonshivering thermogenesis: the relative importance of shivering and nonshivering thermogenesis in different species and in different circumstances; the changes in the balance between the contributions of shivering and nonshivering thermogenic processes during postnatal development and during acclimatization to cold stress; the role of nonshivering thermogenesis during arousal from hibernation and other

forms of torpor; the neuronal and hormonal control of shivering thermogenesis; and the biochemistry of non-shivering thermogenesis.

The assembly of this small group of experts in Prague last year has resulted in the publication of a comprehensive, authoritative and eminently readable series of essays that can be confidently recommended to anyone who needs a relatively painless introduction, or re-introduction, to this exciting field of study.

Although, generally speaking, verbatim reports of the discussions which follow contributions to colloquia are of little value, in this instance I have found the discussions well worth attention. Subsequent reference to this volume will be hampered by the absence of an index. The English is not quite impeccable, but as one who cannot read with confidence in other languages I have nothing but praise for the high standard of Dr Jansky's editorial efforts as well as for his own important contributions to the study of nonshivering thermogenesis.

JOHN BLIGH

Mature Fruit

The Biochemistry of Fruits and their Products. Vol. 1. Edited by A. C. Hulme. (Food Science and Technology: a Series of Monographs.) Pp. xviii+620. (Academic: London and New York, November 1970.) £10; \$30.

As part of a series on food science and technology, the editor quite properly warns that in this book the term "fruit" is to be used in the strictly commercial sense and that, even so, only those fruits most important from an economic standpoint have been chosen. The less-specialized reader will be encouraged to know that in this first, general volume, the contributors have been allowed to step outside this limit if required by their theme; even *Rosa* appears here and there.

Again, although the primary study is to be of the maturation, post-harvest physiology, senescence and storage of fruits rather than of their growth processes, a short section on growth and pre-harvest factors is provided. It was indeed here that I found a chapter which seemed to me to be of outstanding merit—"The Physiology and Nutrition of Developing Fruits" by E. G. Bolland. This writer describes, in terms ranging from molecular to morphological, how mature fruits achieve this status, and also their relationship with the parent plant. The reader may profitably begin with this section.

It will already have become obvious that, fortunately, Dr Hulme believes that fruit biochemistry and physiology "cannot usefully be separated". Nor

should they be bereft of a background in intracellular and higher levels of structure. One hopes that these latter will find a place in the second volume, which is to present the biochemistry and physiology of individual fruits or types of fruit, and also the biochemistry of fruit processing.

This volume makes a classical approach though the constituents of fruits, with chapters on sugars; hexosans, pentosans and gums; pectic substances; organic acids; amino-acids; proteins; enzymes; lipids; volatile compounds; fruit phenolics; carotenoids and triterpenoids, and vitamins. Then comes the section on growth and pre-harvest factors, including hormonal factors, followed by the ethylene factor, the climacteric and ripening. The book ends with a brief consideration of the physiological disorders of fruits.

There are some shortcomings; for example, although chemical constituents are well covered in the subject index, it is less complete in other respects, and when the number of structural formulae in a chapter exceeds seventy the use of Roman numerals is cumbersome. But in general the editor and contributors are to be congratulated. Rarely may the old phrase of "filling a long felt need" be aptly applied: it is well and efficiently earned in this case.

G. A. D. JACKSON

A Big-bang Universe?

Modern Cosmology. By D. W. Sciama. Pp. viii+212+18 plates. (Cambridge University: London, September 1971.) £3.60; \$8.95.

THIS is a survey of the modern developments in cosmology, intended, according to the author, for "readers with only a modest knowledge of mathematics and physics". It is well illustrated with diagrams and photographs and makes interesting reading even for an expert in the field.

The book is divided into sixteen chapters with a theoretical chapter at about the half-way stage on the models of the universe. For the benefit of the non-specialist the first five chapters provide a general description of stars, the Milky-Way system, the external galaxies, radio sources and the quasistellar objects. The associated astrophysical processes such as thermonuclear reactions, cosmic rays, X-rays and γ -rays, neutrinos, gravitational waves, magnetic fields are also briefly described. The next two chapters discuss the observational data on the distribution of radio galaxies and the quasistellar objects. Then comes the theoretical discussion of the simplest cosmological models. For simplicity there is a brief mathematical discussion which is based on the Newtonian laws of gravitation and

motion, in spite of their limited validity. The results from the less ambiguous but more complex theory of relativity are then quoted—and in many ways they are similar to the Newtonian results. With these models in mind the author looks at further astronomical data in the following eight chapters. This largely includes evidence (or lack of it) for the intergalactic matter, the abundance of elements (in particular the helium-hydrogen ratio) and the observed microwave background. The discussion throughout the book is fairly wide but is not deep enough to satisfy the more curious reader. If he wants further information he must look to the more technical reviews available or to the original articles. But, alas, this book does not give references to guide such a reader!

A typical reader is most likely to come to the following conclusions: (1), the redshifts of the quasistellar objects are of cosmological origin; (2), the microwave background is of *primaeval* (big-bang) origin; and (3), the steady state universe is ruled out by the observations. To what extent are these conclusions justified? One may recall Burbidge's recent remark "that views in cosmology at any epoch are largely determined by the ideas of a few strong individuals, rather than by an objective appraisal of the information available" (*Nature*, 233, 36; 1971). Cosmology has come a long way since Hubble observed the redshift from distant galaxies. As this book shows, the observational astronomer has invented numerous ingenious ways of probing the universe. But the environment has limited the precision of his observations when compared with the precision obtained by a laboratory scientist. This in turn has led to ambiguity of interpretation and to numerous controversies. Cosmology, however, thrives on such controversies; for instance, the three statements given earlier are still subjects of controversy, and should not be taken as facts. The criticism that can be levelled against this book is that it does not make the reader fully aware of the controversial nature of the present data. In an earlier book (*The Unity of the Universe*, Faber, 1959), Dr Sciama advanced several attractive arguments in support of the steady state theory. Are the present observations really so unequivocal as to warrant a change of view?

Cosmology was (and even now sometimes is) regarded with suspicion by workers in other branches of science for its lack of actual data and its wealth of ingenious theories. It is hoped that by acquainting the sceptic with the very wide scope of observational cosmology today, this book will correct that impression and will thereby serve a useful purpose.

J. V. NARLIKAR

CORRESPONDENCE

Doomsday Syndrome

SIR,—In the article by John Maddox on "The Doomsday Syndrome" in *Nature* for September 3 (233, 15; 1971) it is said that the current alarm about the effects of exhausts from supersonic aircraft on ozone levels in the stratosphere is quite unfounded. It seems to me that this statement does much less than justice to the calculations by Harold Johnston (*Science*, 173, 517; 1971). His very sober and detailed calculations of course involve a very complicated set of equations. He may have made errors, or may have overlooked some factors, as he himself is careful to admit. It would seem to me that Johnston's calculations are an excellent example of the proper use of basic scientific knowledge in considering the impact of a new technological development. Like any scientific contribution, this is open to criticism and revision; but surely it is far better to raise these issues, and thrash them out, before building a fleet of commercial SSTs rather than after.

As to Mr Maddox's larger thesis, I am not one of those who is crying out "Doom within the Decade", but as far as keeping the world a livable place is concerned I regard present trends as extremely ominous. As one example, I suspect a survey of the world would show a steady increase, over the last half century and more, in the amount of land that is becoming desert or semi-desert. The Israelis, of course, are reversing this trend in their own small country; but the net trend, on a world wide basis, seems certainly to be for the deserts to increase. I spent nearly three months in Australia last year, and enjoyed it immensely; but the more thoughtful and well informed Australians evidently think that this is happening to them. It has certainly happened in the Middle East, in many parts of the Mediterranean Basin, and elsewhere, throughout the course of human history; but I suspect that modern technology, and the need of feeding a rapidly rising population, are accelerating the process. I want to see mankind develop a world that will be at least as good to live in a hundred years hence, or ten thousand years hence, as it

is today. I am not giving way to despair, and I believe in working to change what I see as the present trends; but I cannot be an optimist.

Yours faithfully,

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Research and Development

SIR,—Professor S. Luria's assertion (*Nature*, 233, 171; 1971) that the only option for control is at the level of development of technology and not of basic research should be accompanied by a clarification as to who should be responsible for the control. Should general citizens participate in the decision-making (and I believe they should), then they could do a proper job only if the possibilities of innovations emerge from the basic research at such a slow rate that they can keep up with the ideas about novel developments in science. Otherwise, the development of technology cannot be properly assessed.

As regards the control of basic research, these days most of the scientists cannot conduct the work on their own private funds, and some organizations are required to allocate public money to individual scientists. Since there are always more competent scientists with curiosity and more ideas than available funds, some sort of control has been, is, and will always be exercised. The crucial point then does not lie in the unrealistic question as to whether or not to impose a control on basic research, but what type of control should be chosen for whose benefit on both research and development.

Yours faithfully,

A. SIBATANI

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Insecticides

SIR,—Of three articles on insecticides in *Nature* of October 15, 1971 (leader on "DDT may be good for people" on page 437, Norman Borlaug's support for the pro-DDT lobby on page 444, and "Pyrethrin prospects" on page 441), the last will be the most encouraging to many biologists. Your leader and Norman Borlaug appear to miss one important point—that the proposed banning of DDT in the USA will stimulate the search for better insecticides and integrated pest control which involves biological as well as chemical methods adapted to the ecosystem concerned. Efforts in these directions remain at a relatively low ebb so long as the bludgeon of DDT and other persistent synthetics is readily available. In the words of IBP's Working Group on Biological Control which includes a number of leading specialists on pests and which met in September 1971 at Canberra, there is "increasing realization that the recent era of nearly sole reliance on pesticides for insect control has been a major failure—due to the attendant problems of pesticide resistance, inducement of secondary pest species, the ever-increasing need for more pesticides (pesticide addiction) and mounting costs, yet poor insect control and severe harm to non-target species and the environment. In short, a more ecological approach has become a recognized necessity".

Few would go so far as to recommend the banning of DDT on a world basis until better methods become available and cheap. The present day leaders of developing countries are really too intelligent to follow the example of the USA blindly, as Borlaug suggests they would.

Yours faithfully,

E. BARTON WORTHINGTON

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Should books be prohibited on the grounds that such a step would stimulate the search for better methods of communication?—Editor, *Nature*.

Announcements

University News

The personal title of professor of parasitology in the **University of Birmingham** has been conferred on **Dr J. Llewellyn**.

Lord Todd of Trumpington and **Mr J. R. Colville** have been elected into honorary fellowships in Churchill College, **University of Cambridge**.

The title of professor emeritus has been conferred on **Professor Raymond Smart**, in recognition of his services to **Heriot-Watt University**.

Dr C. P. Whittingham, Rothamsted Experimental Station, has been appointed visiting professor in the Department of Botany and Plant Technology, Imperial College, **University of London**.

Dr G. D. B. Jones has been appointed to a chair of archaeology in the **University of Manchester**.

Dr S. W. Glover, MRC, Edinburgh, has been appointed to the chair of genetics in the **University of Newcastle upon Tyne**, and **Dr F. Goodridge** has been appointed to a personal professorship in electrochemical engineering.

Dr T. H. Hanna has been appointed professor of civil and structural engineering in the **University of Sheffield**.

Dr D. H. Wright, University of Birmingham, has been appointed to the chair of morbid anatomy and experimental pathology at the **University of Southampton**.

Appointments

Professor R. C. O. Matthews, University of Oxford, has been appointed chairman of the **Social Science Research Council** in succession to **Mr Andrew Shonfield**.

Dr Max Milner has been appointed secretary of the **Protein Advisory Group of the Food and Agriculture Organization**.

Miscellaneous

Professor Preston E. Cloud, University of California, has been awarded the **Paleontological Society medal**, in recognition of his research in the biological aspects of Earth history.

The 1971 **Van den Berghs and Jurgens nutrition awards** have been won by **Mr R. J. C. Stewart**, London School of Hygiene and Tropical Medicine, **Dr C. R. Paterson**, University of Dundee, and **Dr J. K. Howard**, Liverpool Health Department.

Entries are invited from candidates under thirty years of age for the 1972 **Maccabean prize**, which will be awarded for an essay on some aspects of the history of medicine or pharmacy. Further information can be obtained from **Dr**

J. K. Crellin, Wellcome Institute of the History of Medicine, 183 Euston Road, London NW1.

International Meetings

November 16–17, **Government, Industry and the Environment**, London (British Institute of Management, Management House, Parker Street, London WC2B 5PT).

November 22–29, **Bulgarian Science and Technology**, London (Sam Black, London Chamber of Commerce and Industry, 69 Cannon Street, London EC4N 5AB).

November 23–25, **Hazards in Construction—an Examination of Causes, Consequences and Costs of Accidents**, London (Conference Office, Institution of Civil Engineers, Great George Street, London SW1).

November 25–26, **Primate Behaviour**, London (Dr R. P. Michael, Primate Behaviour Research Laboratories, Institute of Psychiatry, Bethlem Royal Hospital, Monks Orchard Road, Beckenham, Kent).

November 29, **Practical Data Preparation**, London (Conference Department, The British Computer Society, 29 Portland Place, London WIN 4AP).

December 1, **Non-destructive Testing**, Harwell (Dr P. Hawtin, Chemical Engineering Division, Building 351.15, AERE, Harwell, Didcot, Berkshire).

December 15–17, **Organisms and Continents through Time**, Cambridge (Dr C. P. Hughes, Department of Geology, Sedgwick Museum, Downing Street, Cambridge CB2 3EQ).

Errata

In the News and Views article "Living Longer" (*Nature*, 233, 162; 1971), the two statements attributed in the eighth paragraph to **Dr R. D. Clarke** were communicated by **Dr R. W. Prehoda**.

In the article "Role for Ferredoxins in the Origin of Life and Biological Evolution" by **D. O. Hall**, **R. Cammack** and **K. K. Rao** (*Nature*, 233, 136; 1971), Table 1 should read as follows:

Table 1 Amino-acid Composition of Type 4 (Plant) Ferredoxins

Amino-acid	1	2	3	4	5	6	7	8
Lysine	3	5	4	4	4	5	5	4
Histidine	1	1	1	1	2	1	1	1
Arginine	1	1	1	1	1	1	2	1
Tryptophan	0	0	0	0	0	1	1	1
Aspartic acid	13	14	12	9	14	10	11	13
Threonine	7	6	10	7	6	6	4	8
Serine	6	7	8	8	8	8	7	7
Glutamic acid	13	15	10	16	9	15	16	13
Proline	4	3	4	4	5	4	5	4
Glycine	12	6	7	9	9	9	6	6
Alanine	9	11	10	6	7	6	7	9
Cysteine	5	4	6	4	5	5	5	5
Valine	4	6	5	6	5	10	6	7
Methionine	1	1	1	1	2	0	0	0
Isoleucine	6	5	3	5	6	4	4	4
Leucine	9	9	7	8	7	6	10	8
Tyrosine	3	4	4	2	3	4	3	4
Phenylalanine	1	3	3	4	4	2	3	2
Total amino-acids	98	101	96	95	97	97	96	97
References	*	23	24	18	25	26	27	28

Reports and Publications

not included in the *Monthly Books Supplement*

Great Britain and Ireland

Bulletin of the British Museum (Natural History). Geology. Vol. 20, No. 4: The Ordovician Trilobite Faunas of the Builth-Llandrindod Inlier, Central Wales, Part 2. By Christopher Paul Hughes. Pp. 115–182 + 16 plates. £4.15. Vol. 20, No. 5: Palaeozoic Coral Faunas from Venezuela, I. Silurian and Permo-Carboniferous Corals from the Mérida Andes. By C. T. Scrutton. Pp. 183–227 + 8 plates. £2.40. (London: British Museum (Natural History), 1971.) [246]

Higher Education: Planning and Policy. By Dame Kathleen Ollerenshaw. (Old Queen Street Paper.) Pp. 16. (London: Conservative Central Office, 1971.) 10p. [256]

PEP Broadsheet No. 527: Opting out of the NHS—a Review of the Private Sector of Medical Care. By Michael Lee. Pp. iv + 28. (London: Political and Economic Planning, 1971.) 50p. [256]

The Prospects for a European Security Conference. By Michael Palmer. (European Series No. 18.) Pp. 107. (London: Chatham House, and PEP, 1971.) £1. [256]

Department of Education and Science. Physical Education for the Physically Handicapped. Pp. 28 + 40 figures. (London: HMSO, 1971.) 40p net. [256]

The Lister Institute of Preventive Medicine. Report for 1971. Pp. 32. (London: Lister Institute of Preventive Medicine, 1971.) [256]

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- John Innes Institute. Sixty-first Annual Report. Pp. 88. (Norwich: John Innes Institute, 1971.) 30p. [27]
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